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PRELIMINARY REPORT OF A CASE OF MIXED SEX. AN APPARENT MALE, WITH A TESTIS IN SCROTUM ON RIGHT SIDE; OVARY, TUBE AND UTERUS IN INGUINAL CANAL ON LEFT SIDE

By Hugh H. Young

(From the Brady Urological Institute, Johns Hopkins Hospital)

The following case is apparently the first of its kind to be put on record and is of so extraordinary a character that this brief preliminary report seems desirable. No. 12181. B. U. I. X. Aged 18 years, single. Admitted February 23, 1924, complaining of an undescended left testicle, with malformation of the penis and urethra. His family and past histories are essentially negative. He has had the usual diseases of childhood. At the age of five he had periostitis of the left fibula. He has never had any venereal diseases, but has never attempted intercourse. Aside from the abnormalities of the genitalia described in the physical examination, the patient has had all the normal sex characteristics of the male. The type of bony structure, breast formation, character and tone of voice have all pointed towards a marked preponderating influence of the masculine form of secretion. From early childhood he has liked the forms of play that are so closely associated with boyhood. While at school he played football until he had to stop because of an injury. He is very fond of boxing and baseball. Last winter boxing was his special hobby, and he is said to be one of the best boxers at the school which he attends. At the age of twelve he began to have erections, at which time, because of the nature of its deformity, the penis was always bent downward. About this time he developed an interest in girls and enjoyed dancing with them. As he has grown older he has been "fond of love affairs with girls," and when he has been allowed liberties with them his passions have been excited, and he has had marked erections of the penis. He has never attempted sexual

intercourse, although the desire has been marked. So far as can be determined, his reactions towards girls have been those of a normal young man. He says that a year ago he experienced one nocturnal emission, during which he thinks there was a slight discharge of fluid. He has had no similar experience before or since. There is no history of loss of blood from the urethra or of anything suggesting vicarious menstruation. Very early he discovered that the left testicle was undescended, and also that the urine came out from an opening several inches behind the end of the penis. Three weeks ago, following a dance, the patient had pain in the "undescended testicle" in the left groin. He states that following active exercise at the dance he felt a sensation as if the testicle was trying to get out into the scrotum. Since that time he has continued to have pain, particularly on exercising, and he has had to use pressure to push the contents of the canal upward in order to get relief. The pain which the patient experienced from the mass in the left inguinal region (which at operation proved to be female adnexa) was not periodical in nature, nor were there any external forms of hemorrhage accompanying it. He has had no periodic malaise or other forms of disturbance.

Present Illness.—The patient complains of congenital malformation of the penis, urethra and scrotum. For three years he has had pain in the left groin and notices a "lump" which he thinks is a testicle trying to descend through the external ring into the scrotum. On exercise this causes him pain, but on reducing the lump with pressure the pain disappears. He also desires correction of the malformation of the penis and wants the urethra to be brought out to the end. He has no urinary symptoms and his general health is excellent. He is at present attending school at which he has a good record as an athlete.

February 23, 1924. *Examination.*—The patient is a strong healthy looking young man, about 5 feet 11 inches in height, weight 144 pounds. Well built, and muscular. Chest that of a strong athletic young man. Usual hair in axillae and pubic region. Penis well developed. Mammillary region typically masculine. Chest and abdomen negative. In the left inguinal region there is a rounded, movable mass apparently in the inguinal canal. This becomes large on coughing or straining and painful—it can be reduced by gentle pressure. The left external inguinal ring is a little larger than the right and admits the tip of the little finger; there is an impulse on coughing. The right inguinal ring is normal and there is no impulse on coughing.

Genitalia.—There is a marked hypospadias present with considerable congenital chordee. The penis is held downward and markedly curved. The glans touches the upper end of the right testicle. There is no penile urethra, and the urinary meatus is in a cleft of the scrotum about 5 cm. distant from the glans. The orifice of the urethra is fairly large, and the patient passes a good stream. Between the urinary meatus and the glans there is a narrow firm cord which forms a bow to the markedly arched corpora cavernosa. On the under surface of the glans is a small furrow representing the urethra, and a large hooded foreskin is present. The right side of the scrotum is normal in size and appearance. The right testicle is normal in position, but the outlines are difficult to make out owing to the marked irregularity of the structures. It is impossible to make out definitely the limits of either the epididymis or of the testicle. There is a small hydrocele present, and the rest of the mass in the scrotum measures about 5 cm. in length, 3 cm. in diameter, is somewhat irregular, slightly nodular or lobulated, generally ovoid in shape. The veins are normal in size. The vas deferens is not indurated and is apparently normal. The right external ring and groin are normal. The left side of the scrotum is empty, and consists simply of a flabby thin pouch of skin. The testicle, epididymis, veins and vas are absent.

Rectal.—Anal sphincter normal. The prostate is difficult to outline. It is apparently much smaller than normal, slightly indurated and slightly adherent. It is thought to be an undeveloped or atrophic prostate. The right seminal vesicle is not palpable. The tissues are very indefinite in that region and much less than normal. On the left side one feels an ovoid elastic mass two or three inches above the prostate, soft and very indefinite. Low down near the prostate nothing suggesting a vesicle can be made out. There are a few adhesions along the pelvic wall, but nothing suggesting ampullae can be made out. The triangular ligament is normal. The bulb of the urethra is atrophic or absent. Cowper's glands cannot be felt. The total length of the urethra is very short.

Urinalysis.—Normal.

Prostatic secretion could not be obtained by massage.

Impression.—Strong, healthy, well developed young man. Normal characteristics in every respect. Extensive hypospadias with bifid scrotum, perineal opening of urethra, bulb absent. Left testicle undescended, located in the inguinal canal, painful. Right testicle in normal scrotal sac, peculiar in shape and irregular in outline, impossible exactly to recognize the outlines of the testicle and epididymis. Prostate very small, undeveloped. The right seminal vesicle is palpable, but small. Left testicle absent. High up in that region is a soft oval mass. Penis well developed in size and length. Glans, foreskin, corpora, all about normal in size and consistence. No penile urethra present. Penis held in marked curvature by congenital fibrous band; this is accentuated greatly on erection.

Operation decided upon. First, to restore the undescended testicle to its proper position in the left side of

the scrotum. Second, to correct the congenital chordee by a Heineke plastic. Third, at subsequent operations to form a penile urethra by a Duplay plastic.

February 25, 1924. *Operation.*—Dr. Young. Gas, oxygen and ether.

1. *Operation for supposed undescended testicle of left side.*—An incision about three inches long was made over the inguinal canal which was opened and a fairly large hernia sac discovered and brought out. This contained an irregular mass, on the inferior surface of which could be felt a mass of veins supposed to be the spermatic cord. The vas could not be felt. When the neck of the sac had been freed and thoroughly drawn outward, it measured about 2 to 4 cm. in diameter and 10 cm. in length. The sac was then freely opened and the contents turned out. To our amazement it contained not a testicle as expected, but a very definite normal ovary and tube and what looked like an embryonic uterus. Dr. T. C. Cullen, who was present at the operation, gives the following brief description:

(Special note by Dr. Cullen on the contents of the sac of the left inguinal hernia). "On the inner side there lies the uterus which blends with the peritoneum of the sac and is about 3 cm. in length. At its upper part there is thickening of the peritoneum. The uterus at the fundus is about 2 cm. broad, 1 cm. thick, and tapers down to what may be the cervix, which is about 1 cm. in diameter. From the fundus at the upper side a Fallopian tube passes off. This is six inches long and looks perfectly normal. The fimbriae are unaltered. The ovary measures 5×3×2 cm. and contains a freshly ruptured corpus luteum. The parovarium looks normal. The forecast is that we shall find the same thing on the right side. The round ligament, instead of starting at the fundus, apparently begins about 2.5 cm. below the tubular insertion and passes down by the side of the cord above described."

2. At this moment the problem seemed to me to be as follows: A normal-looking young man with masculine instincts was found to have a normal tube and functionating ovary in the left groin. What was the character of the scrotal contents on the right side? If these were also undoubtedly female, should they be allowed to remain outside in the scrotum? If a male, should the patient be allowed to continue through life with a functionating ovary and tube in the abdomen on the left side? If the organs of either side should be extirpated, which should they be? It seemed imperative, therefore, to make an incision in the right groin to determine the nature of its contents. An incision was made about 2 inches in length, and the scrotal contents delivered. They were covered with a normal dartos. The veins were large; no vas could be felt or discovered after several incisions and a very careful examination of the cord. There was a small hydrocele present. The tunica vaginalis was opened out and was found to be quite redundant but otherwise normal. Within the sac lay a body larger than the normal testicle, somewhat irregularly lobulated with depressed, indurated, pale areas, the intervening bulging portions being rather softer than normal testicle. The gonad (it was impossible to say whether it was testicle or ovary because it looked typically not like either) measured 5 cm. in length and 2.5×3 cm. in diameter. It was invested by a tunica albuginea except posteriorly where the veins of the cord entered. Externally to this in the position of the epididymis lay a peculiar tubule-like structure which was only loosely attached to the testicle by a "mesentery" from 1 to 2 cm. in length. This structure presented a club-shaped end about 1 cm. in diameter, on the tip of which was a peculiar red, sessile, soft structure unlike anything I have ever seen. It did not resemble the fimbriated end of a tube. The rest of the structure beyond the club-shaped end tapered down to a small tube, 3 or 4 mm. in diameter, which extended for a distance of about 4 cm. where it ended in a peculiar body which lay beneath the tunica vaginalis. The outlines of this body were indefinite. In consistence it was fairly firm (it was subsequently removed for examination). Running upward and backward from this body two very small fibrous cords were seen beneath the tunica vaginalis. Careful examination showed that these were not tubular (they contained no lumen). As these tubes passed upward they seemed to coalesce where they joined the spermatic vessels in the cord, but from that point they disappeared and nothing suggesting a vas deferens could be found on very careful examination. Dr. Cullen gave his opinion as follows: "The large body is, I believe, an ovary. Behind it is a tube, and the peculiar body on the end of this is the fimbriated end. On the other end of the tube the peculiar subserous body is the undeveloped other half of the uterus."

The supposed ovary was, however, entirely unlike the normal and nothing suggesting corpora lutea could be seen (such as were present on the opposite side).

As the question was one of great importance, it seemed wise to excise a fairly large section of the upper end of the gonad in order to determine its character. This was done. A piece about 2 cm. in diameter and almost 1 cm. thick being removed. Frozen sections were made and examined by Dr. TeLinde, assistant resident gynecologist, who reported that it was certainly not an ovary. It contained tubules, epithelial and interstitial cells which Dr. Davis thought were undoubtedly testicular. It was then decided to restore the scrotal contents on the right side, but before so doing the peculiar body, supposed by some to be an infantile uterus, was excised from its location in the tunica vaginalis, on the right side. The testicular wound was then closed with catgut, the tunica vaginalis turned inside out and sutured behind the testicle (as in the operation for hydrocele), and the scrotal contents were

returned. The subcutaneous fascia was closed with catgut and the skin with metal clips.

It was determined to preserve the masculine contents of the right scrotal sac. It seemed obvious, therefore, that the only thing left was to remove the female contents of the left hernia sac. This was accordingly done. The hernia was removed completely and brought with it the ovary, tube and uterus, the point of division being about 2 cm. distant from the cervix. In making this division a large group of veins were ligated and divided. Two small muscle-like structures and one tube, exactly the size and consistence of the vas deferens were divided. This tube and the two cords lay beneath the peritoneum, and the general direction was towards the pelvis by the side of the bladder.

A brief pathological report (by Dr. D. M. Davis) of the microscopic study of some of the sections follows:

Hurried sections were made of this tissue at the time of presentation before The Johns Hopkins Hospital Medical Society on Monday, March 3, 1924. These sections show definite ovarian structures in the ovary-like organ, from the left groin, whereas in the other gonad from the right side of the scrotum there are very definite seminiferous tubules. The ovary is apparently active, and ova and Graafian follicles are present. The testicular tubules are apparently inactive, being lined with undifferentiated cells and showing no spermatocytes, spermatogonia or spermatozoa. Between the tubules are very large masses, comprising the greater part of the section, of cells with rounded vesicular nuclei; the nature of which is uncertain. Some of them are hydropic and show a large amount of clear transparent cytoplasm. It is possible that they represent an enormous hypertrophy of the interstitial gland. The Fallopian tube and uterus, taken from the left groin, are normal in appearance. Further notes will be made when the permanent sections are finished.

This case is unique for two reasons:

1. It is the *first human* case of true lateral glandular hermaphroditism recorded.

2. Unlike all the lateral hermaphrodites found *in animals*, our patient is *masculine* externally, though he has inactive tubules and a functioning ovary. The interstitial cells are, however, apparently hyperplastic and no well developed lutein cells are seen.

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A PRELIMINARY STUDY OF THE BLOOD-PRESSURE FOLLOWING REDUCTION OF RENAL SUBSTANCE WITH A NOTE ON SIMULTANEOUS CHANGES IN BLOOD-CHEMISTRY AND BLOOD-VOLUME

By James R. Cash

(From the Department of Pathology, The Johns Hopkins University, Baltimore)

Since we now possess a satisfactory method for measuring the blood-pressure over long periods of time, in the intact, unanesthetized dog, it was felt that the attempt to alter the blood-pressure experimentally might yield information of value. The present study is based upon a series of only ten dogs but, as several rather startling facts seem to have appeared, it is felt that a presentation of them at this time, without any attempt at generalization, may arouse interest in what now appears a very fruitful field for experimentation.

These experiments were begun with the attempt to produce a renal insufficiency, by excision of kidney tissue, in previously normal dogs upon which studies of blood-pressure, blood-chemistry, and blood-volume had been made; after operation these studies, in most instances, have been continued for two to four months. Dogs of both sexes, weighing from ten to thirty-five pounds, were used. The animals were kept in the same room, in large single cages and fed with dog-biscuit and ground meat; the weight of each animal was followed closely before beginning any experiments and the proper amount of food determined which was necessary for the maintenance of proper nutrition. Food in slight excess of this amount was given daily and, during the period of normal observations, most of the animals, although already well nourished, gained weight slowly. Thus, the diet, though far from an accurate one, was practically constant. One thousand cubic centimeters of fresh water was supplied twice daily and a record kept of the amount consumed every twenty-four hours. The urine was collected once a day and the amount and specific gravity recorded; from time to time microscopical urine examinations were made. Samples of blood for chemical analysis and blood-volume estimations were

taken only after twenty-four hours' fasting; the non-protein nitrogen and total chlorides of the whole blood were determined routinely and observations of creatinine, sugar, and carbon-dioxide combining power were frequently performed. These analyses were made in the chemical laboratory of the Johns Hopkins Hospital. The recent "brilliant vital-red" dye method [1] was used for the blood-volume determinations.

After the animals had been kept under experimental conditions for about a week the normal observations were begun. Quiet dogs were selected and blood-pressure determinations were made until it was felt that a representative average of both systolic and diastolic pressure had been obtained. It had previously been noted, in observation of the normal blood-pressure of the unanesthetized dog,[2] when quiet animals are used, that the average of the first ten or twenty observations, extending over a period of four or five days, does not vary appreciably from the average of long series of observations extending over several months' time. Consequently, a smaller number of normal blood-pressure determinations were done upon the latter animals of this series.

The blood-pressure observations were made with the apparatus described recently by Kolls.[3] It consists of a specially designed sphygmograph of great delicacy connected to a rubber bag and metal cuff, which fits the upper hindleg, and a mercury-manometer bearing a writing point. After being closely applied to the leg, the bag, which lies on the inner surface, is inflated to a point well above systolic pressure, thus completely compressing the femoral artery. At this high level the pulsations of the proximal end of the artery are recorded on a smoked drum by the sphygmograph as minimal oscillations, since the impulses are transmitted to the rubber bag at one small point only. By dropping the pressure a few millimeters at a time, systolic pressure, the pressure at which blood begins to penetrate beneath the bag, is reached. At this point the section of artery, hitherto completely compressed by the bag, begins in turn to compress the bag by its expansion and, accordingly, the oscillations of the sphygmograph, whose amplitude depends upon the excursion of the arterial wall, suddenly increase. When the pressure within the bag is further reduced the oscillations gradually reach a maximal amplitude as the artery is allowed more room for expansion and then decrease progressively at lower levels. Maximal oscillations can occur only when the pressure within the bag by which the artery is compressed is just exactly the diastolic pressure, for, at levels above this point, the maximal excursion of the arterial wall from diastole to systole cannot occur, while below this point the artery is not completely compressed in diastole and the excursion made by its wall, while passing to its position in systole, is accordingly reduced. As this optimal point of compression is rarely exactly hit upon in deflating the bag, the pressure at which the first reduction of amplitude occurs is the one usually chosen as diastolic pressure. This method will of course be recognized as that introduced by Erlanger for taking human blood-pressure. The further modifications designed by Kolls consist of a specially designed sphygmograph, cuff and a rubber bag which compresses the leg laterally. As stated in a previous paper,[2] the accuracy of the method has been carefully checked with and without anesthesia, by recording the systolic and diastolic pressures with a maximum-minimum valve connected to a cannula in one femoral artery while indirect determinations were made simultaneously by the method described on the opposite leg.

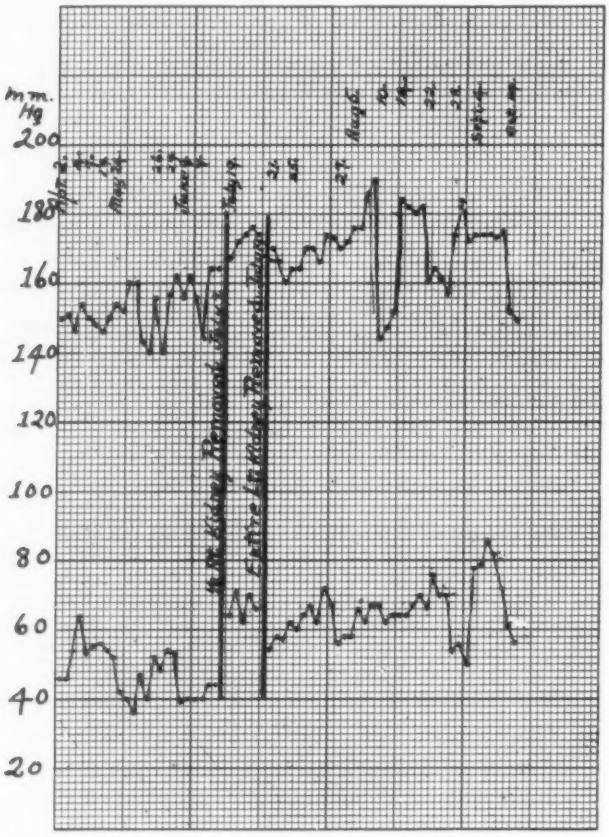
During the period over which normal blood-pressure studies were being carried on, at least three blood-volume determinations and analyses for non-protein nitrogen and chlorides of the blood were done. The phenolsulphonephthalein excretion was determined during this time by injecting one cubic centimeter of the dye intravenously and estimating the amount excreted in the urine obtained by catheterization one hour later.

All operations were performed retroperitoneally through lumbar incisions. When a portion of one kidney was excised this was accomplished by first tying off the part to be removed by interlocking mattress sutures of heavy silk, which, with a blunt needle, can be placed through the kidney with very little haemorrhage. The capsule can then be stripped back to this suture-line and the denuded portion excised. No matter how firmly the sutures are tied, bleeding generally occurs from several large vessels, but these can easily be caught and tied before any serious haemorrhage occurs. In only one animal of the present series (Dog 11) was there any appreciable amount of blood lost. Operating in this manner one does not disturb the remaining part of the kidney, nor is the adrenal injured.

Expt. 1. Dog 11.—Large, female bull-terrier, weight 36.75 lbs. Three-fourths of the total renal substance was removed. At the first operation one-half of the right

kidney was resected. Twelve days later the entire left kidney was removed. Recovery from both operations was uneventful.

Dog 11.—Blood-pressure.



	Normal	After operation	Change
Systolic pressure	152	170	+18
Diastolic pressure ...	48	65	+17
Pulse pressure	104	105	+1

Dog 11.

	Normal	After 1st operation	After 2nd operation						
			1st wk.	2nd wk.	3rd wk.	4th wk.	5th wk.	6th wk.	7th wk.
Fluid Intake C. C. (24 hrs.)	624	953	694	1306	880	1354	1100	880	730
Total Urine C. C. (24 hrs.)	324	340	364	437	606	1160	626	701	492
S. G. Urine	1.031	1.030	1.023	1.017	1.019	1.017	1.016	1.020	1.027

Dog 11.

Date	Weight pounds	Per 100 c.c. blood		Per 100 gm. body weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
April 3..	36.75	30.6	534				
April 8..	36.75	27.9	556	5.17	8.79	41.3%	60%
April 18..	34	26.4	511	6.45	11.4	43.7%	
April 26..	32	40	523	5.95	10.1	41 %	
June 19..		37.2	552				
June 28..	31			5.93	9.5	37.5%	50%
July 5..	30	23.8	521	6.51	11.62	43.9%	
July 7..	One-half of right kidney excised. (Severe haemorrhage.)						
July 19..	Left nephrectomy.						
July 24..		80	546				20%
Aug. 17..		89.5					
Aug. 24..	28.5	70	608	8.0	10.2	21.7%	35%
Sept. 5..	29	50	577	6.98	8.91	21.7%	

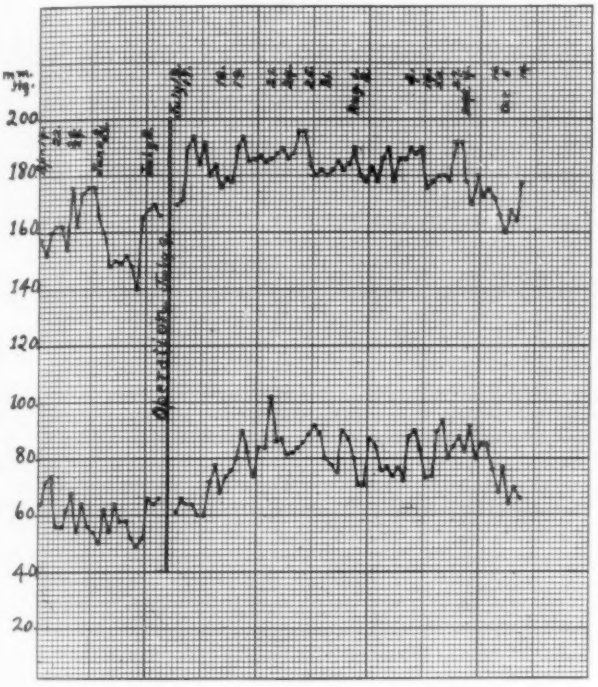
There are several complicating factors in this experiment and it is only of value in connection with those which follow. Soon after beginning the observations the animal contracted mange, which grew progressively worse for some time. The loss of weight in the preoperative period is attributed to this. The mange, however, was completely cured before the first operation. In excising half of the right kidney much blood was lost; accordingly blood-volume observations after this time are not of much value. It is, however, clear that a moderate elevation of blood-pressure occurred after the first operation and has been maintained for about two months. Accompanying this rise of blood-pressure will be noted a slight increase in the nonprotein nitrogen of the blood. That a rise of blood-pressure unaccompanied by such a change in the blood may occur even when larger amounts of kidney substance are removed is shown in the next experiment.

Expt. 2. Dog 12.—Large male bull-terrier, weight 35 lbs.

Since Dog 11 recovered so easily after removal of three-fourths of the total kidney substance, an attempt was made to remove slightly more than this amount. The right renal artery was found to divide at the pelvis into two small branches and one larger one. The two small branches, which apparently passed to the upper pole, were ligated and seven grams of kidney tissue excised from the lower pole. The opposite kidney, which

weighed thirty-four grams, was then removed. Thus, at one operation sixty per cent of the total renal substance was actually excised and twenty-five per cent theoretically destroyed and left within the animal. Practically no blood was lost and the dog recovered quickly without infection.

Dog 12.—Blood-pressure.



	Normal	After operation	Change
Systolic pressure	161	182	+21
Diastolic pressure ...	60	78	+18
Pulse pressure	101	104	+3

Dog. 12.

	After operation					
	Normal	1st wk.	2nd wk.	3rd wk.	4th wk.	5th wk.
Fluid intake c.c. (24 hrs.)	229	534	498	398	370	336
Total urine c.c. (24 hrs.)	240	303	442	388	272	236
S. G. Urine.... (24 hrs.)	1.042	1.028	1.031	1.030	1.038	1.032

Dog. 12.

Date	Weight pounds	Mg. per 100 c.c. blood		C.C. per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
April 18..	35	30	540	5.14	9.4	43.5%	
June 19..		45.8	344				60%
June 27..							50%
July 5..	33.25			5.2	10.1	48.3%	
July 9..	Left nephrectomy. Ligation of two branches of right renal artery supplying upper pole; excision of 7 grams of the lower pole. Total calculated destruction of renal substance was 85%.						
July 17..	31.5	42.5	525	6.24	10.65	41 %	25%
July 21..	31.25	35.9	503	5.73	9.78	41.4%	25%
Aug. 12..	33.5			4.80	8.73	45 %	
Aug. 14..	33.5	40.8	509	4.57	8.65	47.2%	
Aug. 24..	31.5		500	4.85	9.38	47.5%	
Sept. 5..	32	45.4	519	4.55	9.21	50.9%	37%

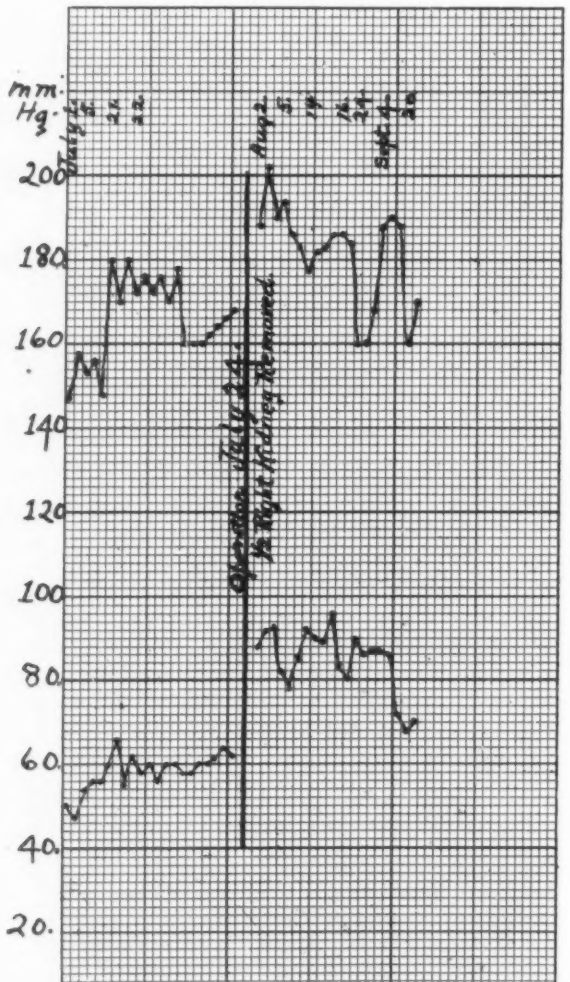
Of course it is impossible to say how much over sixty per cent. of the total renal substance was rendered incapable of function, but it does seem safe to set the figure considerably higher. Theoretically, slightly over one-half of one kidney was left to undergo necrosis within the animal. The blood-pressure rose promptly after the operation and remained elevated for at least eight weeks; during the latter portion of which time it showed a tendency to fall. The phthalein excretion was considerably diminished but no changes occurred in either blood-chemistry or blood-volume. To all outward appearances this dog has not been changed by the operation; there has been no loss of weight and the haematocrit has risen steadily.

In the endeavor to decide what rôle the necrotic kidney substance left within the dogs in the two previous experiments bore to the rise in blood-pressure, the following experiment was performed.

Expt. 3. Dog 16.—Medium sized bull-terrier, female, weight 24.75 lbs. Half of the right kidney was tied off

with a double row of mattress sutures and only a third of this part excised, thus leaving a large denuded mass of kidney tissue which had been deprived of its circulation. No bleeding occurred from the cut surface. The portion of the kidney proximal to the sutures was observed for thirty minutes and no impairment in its circulation noted. At autopsy, performed five months after the operation, it was found that the entire kidney had been destroyed, only a few scattered, greatly altered glomeruli and remains of a few tubules remaining in a dense mass of scar tissue, which measures about 3 cm. in diameter.

Dog 16.—Blood-pressure.



Dog 16.

	Normal	After operation	Change
Systolic pressure	166	182	+16
Diastolic pressure ...	63	85	+22
Pulse pressure	103	97	—6

Dog 16.

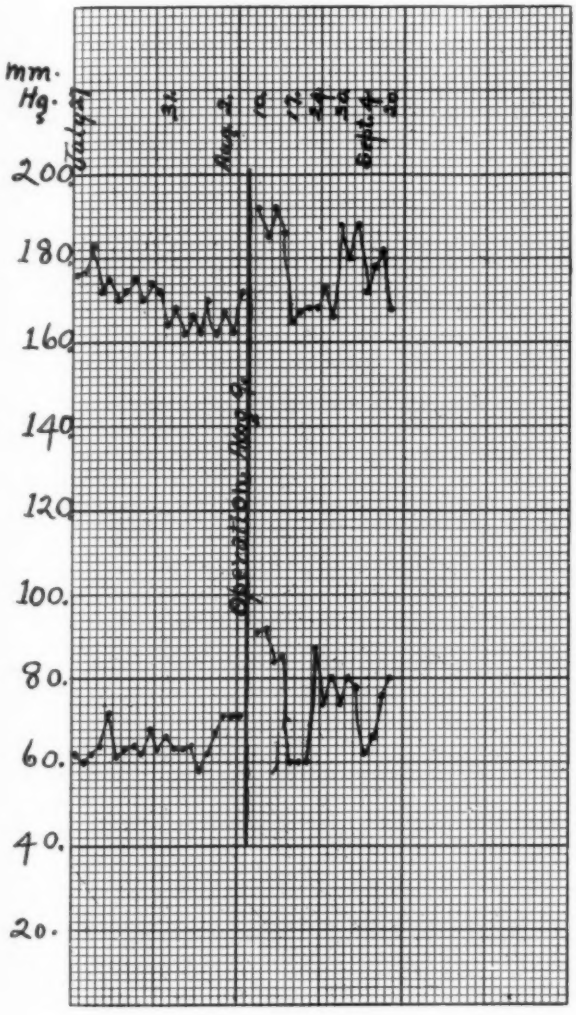
Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
July 3..	24.75	43.2	488	4.78	8.70	45 %	60%
July 6..		44.1	487				
July 8..		27.4	492				
July 18..	25.5			4.79	8.17	42.2%	
July 21..	25.5	33.3	532	4.60	7.83	41.3%	
July 24..	One-half of the right kidney was rendered bloodless by mattress sutures and part of this portion excised. Abscess developed in muscles, and blood-studies were discontinued until this was entirely healed. The total destruction of renal substance was, however, fifty per cent., as shown by autopsy.						
Aug. 16..	24.5	27.7	538	5.55	8.77	36.8%	55%
Sept. 5..	23.0	25.0	523	5.87	8.59	32 %	

This animal was never ill after the operation. The blood-pressure rose promptly and no changes occurred in blood-chemistry, blood-volume, phthalein-excretion, total amount or specific gravity of the urine. It therefore seems improbable that the rise in pressure could have been occasioned by a lack of functioning renal substance alone. On the other hand, it is strongly suggested that the renal substance left to undergo resolution within the body was in some way associated with this change. Here again, as in the previous experiment, there has been a tendency for the blood-pressure to return to its pre-operative levels.

Expt. 4. Dog 19.—Bull-terrier, male, weight 22 lbs. The left renal artery was found to divide at the hilum into two branches of about equal size. The upper one

of these was ligated and one-half of the lower pole of the kidney excised. The entire right kidney was then removed. Thus, sixty-two and a half per cent of the total renal substance was actually removed while twenty-five per cent was theoretically destroyed and left to be absorbed.

Dog 19.—Blood-pressure.



Dog 19.

	Normal	After operation	Change
Systolic pressure	171	178	+7
Diastolic pressure....	66	76	+10
Pulse pressure	105	102	—3

Dog 19.

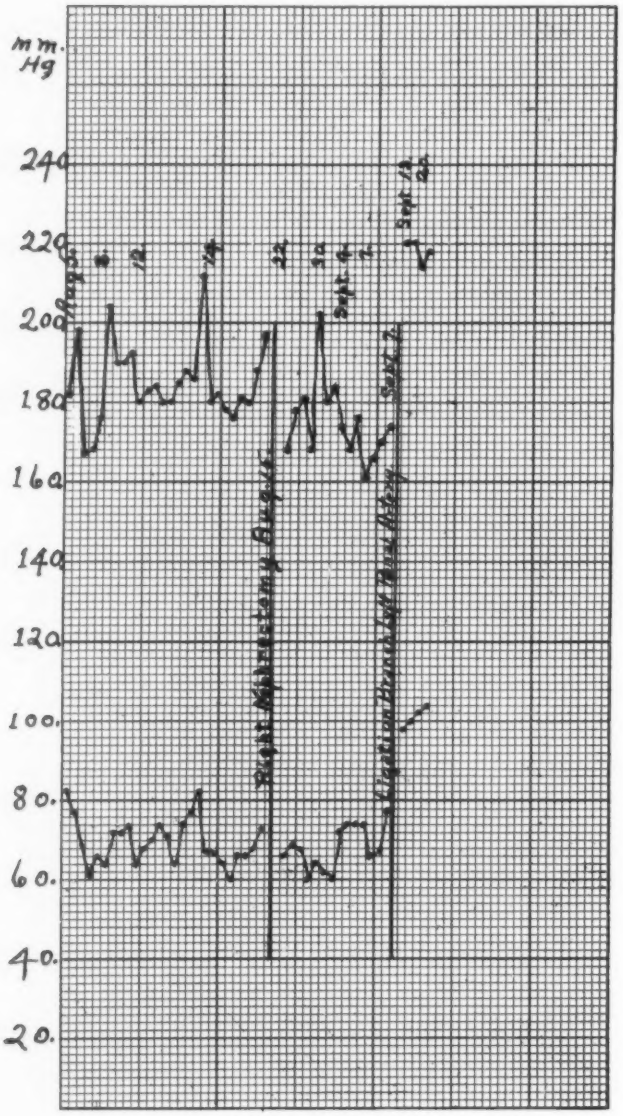
Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
July 28..	22	37.25	511	4.10	7.78	47.2%	
Aug. 3..	25.5	37.5	507	4.62	8.40	45 %	70%
Aug. 7..	25.5	34.1	498	4.53	8.37	45.8%	65%
Aug. 8..	One branch of the left renal artery was ligated and half of the pole whose circulation remained undisturbed, excised—right nephrectomy. Total destruction of renal substance was 87½%. Recovery uneventful.						
Aug. 10..	21.5	98.3	478	4.79	8.23	41.7%	15%
Aug. 17..		85.2	517				
Aug. 29..	18			5.64	9.26	39 %	
Sept. 5..	19	60	503	5.51	9.36	41 %	35%

A moderate functional deficiency of renal substance has been produced in this experiment, as shown by the increase of non-protein nitrogen in the blood and decrease in phthalein-excretion following operation. The plasma volume appears to be slightly increased but these figures lie within the upper limits of normal variation and experimental error. The blood-pressure, however, rose slightly. The dog, on the other hand, appeared quite abnormal after operation. He lost much weight without obvious cause other than the deficiency of kidney substance. Upon being disturbed a violent tremor occurred over the entire body which rendered blood-pressure observations rather unsatisfactory.

In the four preceding experiments a moderate hypertension developed following reductions in renal substance of twenty-five to eighty-seven and a half per cent, and the idea that this rise was in some way connected with necrotic kidney tissue left within the animal strongly suggested. To gain further proof for, or against, this theory it was decided to compare the results obtained in reducing the kidney substance fifty per cent by unilateral nephrectomy and by ligation of one renal artery. If the presence of necrotic kidney tissue is necessary for the production of an increase in arterial tension, those animals suffering the loss of one kidney by nephrectomy should show no rise in pressure, while those in which unilateral ligations are done should develop hypertension. These procedures were carried out in the following four experiments.

Expt. 5. Dog 22.—Mongrel, male, weight 25.75 lbs. August 15th: Right nephrectomy. September 7th: Ligation of one branch of left renal artery.

Dog 22.—Blood-pressure.



	Normal	After right nephrectomy	Change	After ligation of one branch left renal artery	Change
Systolic pressure...	185	174	−11	213	+34
Diastolic pressure..	67	68	+ 1	101	+33
Pulse pressure.....	118	106	−12	102	−10

Dog 22.

Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
Aug. 8..	25.75	46.15	532	5.85	10.25	43.7%	60%
Aug. 14..	25.5	32.25	503	5.90	10.15	41.7%	
Aug. 14..	Right nephrectomy. Recovery uneventful.						
Aug. 15..	24.5	39.9	486	5.95	10.10	41 %	55%
Sept. 6..	Posterior branch of left renal artery ligated. Recovery uneventful.						
Sept. 16..	23	37.5	540	5.76	9.76	41 %	40%

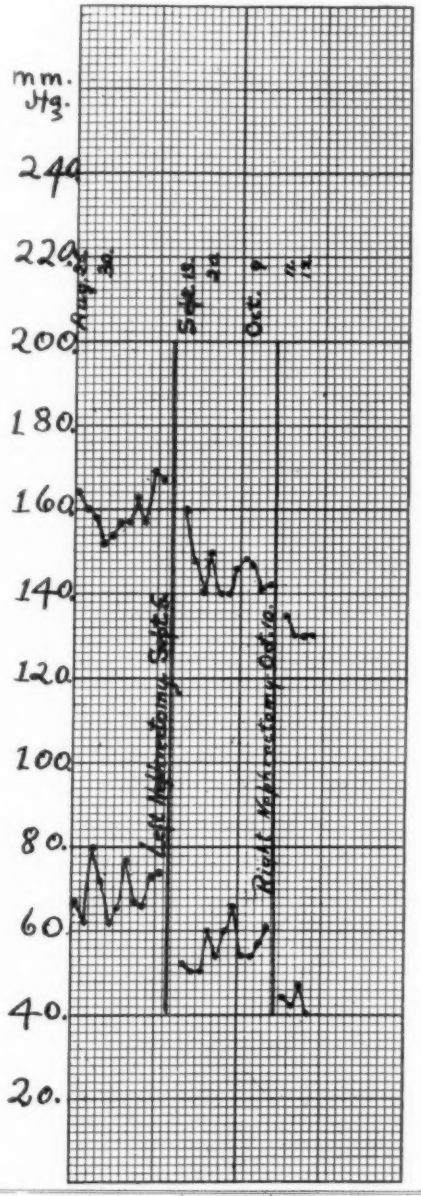
After unilateral nephrectomy no rise of blood-pressure occurred. On the other hand, the dog became much quieter after the operation and a moderate fall of systolic pressure followed, though no change occurred in diastolic pressure. The average pressures observed during this period approach very closely those of dogs determined by previous observations on a series of normal animals. Following ligation of one branch of the left renal artery, however, there occurred a sharp rise of pressure. No changes took place in the blood-chemistry or blood-volume and the phthalein excretion was reduced very slightly. After the first operation the total amount of daily urine, the consumption of water, and the specific gravity of the urine remained unchanged.

It is regretted that only four observations of blood-pressure could be obtained after the second operation. This animal which, until two weeks after this time, was very quiet and in all ways suitable for the experiment then, as dog 19, became very irritable and restless, thus causing any pressure determinations to lose all value. Many attempts were made and though diastolic pressure was found to be elevated, it is not felt that such determinations are of any significance.

Expt. 6. Dog 25.—Collie, male, weight 22½ lbs. After unilateral nephrectomy no rise in either systolic or diastolic pressure occurred. The routine studies of the blood and urine revealed no changes. This animal, also, became much quieter after operation and a corresponding moderate reduction of pressure was noted.

In order to test the effect of bilateral nephrectomy upon the blood-pressure, the right kidney was removed. Accurate readings could be obtained for only two days. A decided fall in both systolic and diastolic pressures was noted during this period. After this the heart became very irregular and the systolic pressure fell below 60 mm., at which level satisfactory observations cannot be made.

Dog 25.—Blood-pressure.



	Normal	After unilateral nephrectomy	Change
Systolic pressure	159	146	—13
Diastolic pressure	70	54	—16
Pulse pressure	89	92	+3

Dog 25.

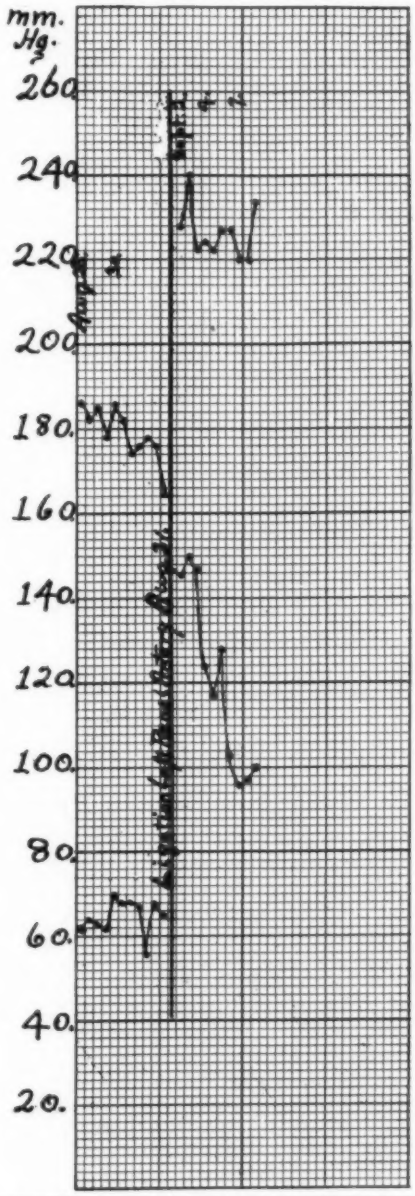
Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
Aug. 29..	22.5			4.90	8.35	41.3%	60%
Sept. 5..	Left nephrectomy. Recovery uneventful.						
Sept. 16..	22.5	42.5	535	6.27	9.97	37.1%	60%
Oct. 9..	21.5	24.1	671	6.2	9.7	36 %	
Oct. 10..	Right nephrectomy.						

Dog 25.—Continued

Oct. 11..		97.6	601				
Oct. 12..		183.0	605				
Oct. 13..		211.0	573				

Expt. 7. *Dog 26.*—Small mongrel, female, weight 10.5 lbs. A marked rise of both systolic and diastolic pressure followed ligation of the left renal artery. No changes occurred in the blood-chemistry, blood-volume or daily amount of urine.

Dog 26.—Blood-pressure.



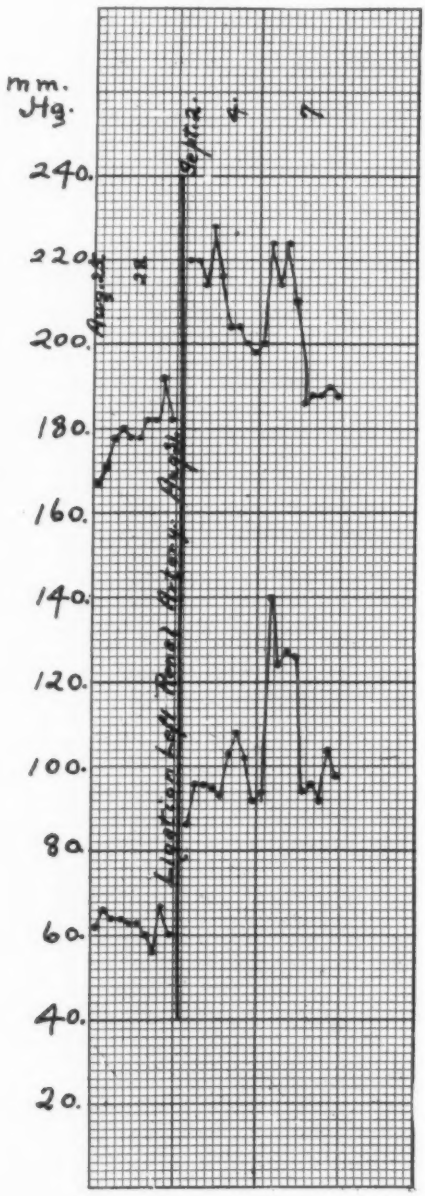
	Normal	After ligation of left normal artery	Change
Systolic pressure	179	226	+47
Diastolic pressure	65	120	+55
Pulse pressure	114	106	—8

Dog 26.

Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
Aug. 29..	10.5			4.8	9.15	47.5%	
Aug. 31..	Left renal artery ligated. Recovery uneventful.						
Sept. 16..	11.5	31	503	5.2	8.9	41 %	60%

Expt 8. Dog 27.—Beagle, male, weight 16.5 lbs. The preceding experiment was repeated with similar results.

Dog 27.—Blood-pressure.



	Normal	After ligation of left renal artery	Change
Systolic pressure	179	206	+27
Diastolic pressure	63	103	+43
Pulse pressure	116	103	−13

Dog 27.

Date	Weight pounds	Per 100 c.c. blood		Per 100 gms. body-weight		Haematocrit	Phthalein
		N.P.N.	Chlorides	Plasma volume	Blood volume		
Aug. 29..	16.5			4.7	8.3	43.2%	60%
Aug. 31..	Left renal artery ligated. Recovery uneventful.						
Sept. 6..	17.5	30	515	5.51	8.57	35.7%	60%

At this point the experiments were interrupted for a period of one year during the author's absence. The dogs lived from three months to one year after the beginning of their respective experiments. Several of them developed marked cachexia associated with formation of stones in the renal pelvis and kinking of the ureter by scar tissue, while others were sacrificed while in apparently good health at the end of a year's time. It is not deemed necessary to include here a description of the complicated chronic changes which were found to have taken place in the injured portions of remaining kidney tissue which, owing to their chronicity, give little light upon the production of the rise in arterial tension. The most valuable result of the autopsies was the proof that the intended injuries to the kidney had been accomplished by the ligations. Only in one case (Expt. 3, Dog 16), was there an exception to this general finding. In this case the intention was to destroy a half of one kidney by interlocking mattress sutures placed across the entire organ; at autopsy the entire kidney was found to be destroyed, only a few shruken glomeruli and remains of scattered tubules being embedded in a small mass of dense scar tissue about two centimeters in diameter. This finding places this experiment in the group of experiments 7 and 8, in which an entire kidney was destroyed by ligation. In the ligated portions of kidney there always remained a few shrunken glomeruli and distorted tubules and some slight collateral circulation had developed as has been described by MacNider[14] in his study of renal infarction in the cat after ligation of branches of the renal artery. The portions of kidney which remained more or less intact showed hypertrophy roughly commensurate with the amount of total reduction of renal tissue.

So far, the salient features of these experiments have been:

(1) A moderate elevation of both systolic and diastolic blood-pressure has attended reductions of renal substance, where varying amounts of kidney tissue have

been deprived of their circulation and allowed to remain within the body.

(2) This elevation of pressure has been sustained for a considerable period of time in all instances, but has shown a tendency to fall where longer series of observations have been made.

(3) There has occurred no associated renal insufficiency, as shown by chemical studies of the blood, but where large amounts of kidney tissue have been removed or rendered incapable of function by ligation of renal vessels, there has been a diminution in the total output of phenolphthalein.

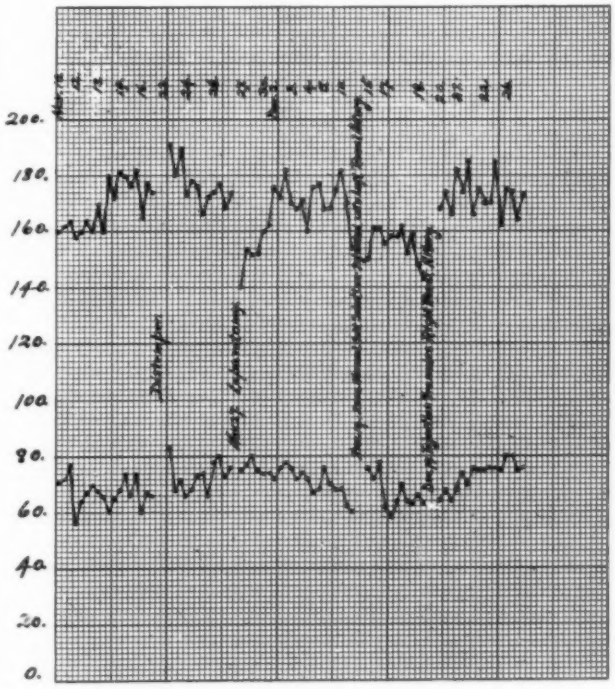
(4) No significant changes have occurred in the blood volume.

The question now arises as to whether the absorption of necrotic renal substance alone is sufficient to cause this elevation of blood-pressure. Should this be the case, the experimental production of many small infarcts in one kidney or the ligation of only one branch of a renal artery without further reducing the kidney tissue should suffice to elicit such a pressor response.

Expt. 9. Dog 30.—Observations of normal blood-pressure were recorded for seventeen days when a laparotomy was performed, both kidneys were slightly traumatized with the hand and the renal vessels rather roughly handled with forceps. This procedure was carried out as a control to determine whether the rises in blood-pressure previously noted were likely to be associated with operative procedures alone. During the following period of thirteen days no material change of blood-pressure occurred. Several rather low readings of systolic pressure were noted but no particular significance is attached to them, since such variations in systolic pressure are commonly seen in almost every long series of observations on normal dogs. Attention is here called to the great variation in rate, force and rhythm of the dog's heart; these irregularities must certainly be accompanied by appreciable changes in the volume-output. This fact is most likely the greatest factor in producing such variations in systolic pressure. The diastolic pressure, on the other hand, remains remarkably constant in quiet animals and, in all of the experiments, much more significance is placed upon any elevation which it may show than upon the changes in systolic pressure.

Contemplating the production of multiple, small, renal infarcts by injection of a granular substance, a second control experiment was performed upon this dog by injecting 20 c.c. of normal salt solution into a renal artery in order to rule out any effect which injection of fluid and the puncture of the wall of the vessel might have on the blood-pressure. For a period of five days no change was noted. Ten cubic centimeters of a suspension of insoluble Berlin blue in normal salt solution was then injected into the other renal artery. During the seven days which followed, the systolic pressure, which, after the injection of salt solution alone had fallen somewhat, rose to its former level but showed no tendency at any time to exceed the normal limits of systolic pressure in the dog. The diastolic pressure remained constant throughout the entire experiment. An autopsy performed a week after the injection of the granules showed many small infarcts in the right kidney; the left kidney and other organs showed no changes. In this experiment necrosis of a considerable amount of kidney tissue has not proven sufficient to produce an elevation of blood-pressure.

Dog 30.—Blood-pressure.

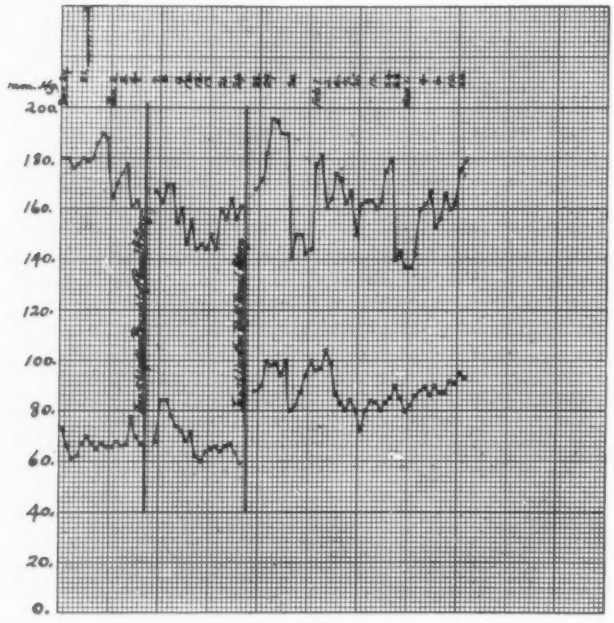


	Normal	After production of infarcts in left kidney	Change
Systolic pressure	167	173	+6
Diastolic pressure	70	73	+3
Pulse pressure	97	100	+3

Expt. 10. Dog 33.—In the previous experiments, where one branch of a renal artery was ligated, this procedure was accompanied by excision of the opposite kidney and in addition, in some cases, by resection of a portion of the partially ligated one. In the present experiment, after a week of normal blood-pressure observations, one of the two main branches of the left renal artery was ligated and observations of pressure recorded for three weeks before any further reduction of kidney substance was attempted. Forty-eight hours after the operation

several rather high levels were reached by diastolic pressure, but during the rest of this interval the diastolic pressure remained at its pre-operative level. The opposite renal artery was then ligated. After forty-eight hours a remarkable change had occurred in the character of the pulse in the femoral artery. This vessel, which previously had been palpated each time the blood-pressure was taken and found to possess a soft wall and to be easily compressed, was felt as a firm, tense cord which offered great resistance to attempts at compression. Instead of the familiar collapsing quality of the dog's pulse, a sustained increase of arterial tension was clearly perceptible. As will be seen from the following chart, a considerable rise of diastolic pressure has been maintained for about eight weeks and a slight tendency to return to the normal level has occurred. No very good explanation can be offered for the marked variations in systolic pressure other than the probable great variation in the volume-output of the heart per beat in the dog. This animal is still living and in good general condition; the blood-pressure will be followed for some time and an autopsy performed at a time deemed suitable for demonstrating maximal hypertrophy of the heart, should it occur.

Dog 33.—Blood-pressure.



	Normal	After ligation of branch of left renal artery	Change	After ligation of right renal artery
Systolic pressure ...	175	156	—19	—11
Diastolic pressure ..	68	69	+1	+21
Pulse pressure	107	87	—20	—32

By these last two experiments several interesting points are brought out. Simple widespread necrosis of renal tissue, such as is produced by numerous small infarcts in one kidney, is not sufficient to produce an elevation of blood-pressure, nor does any change of pressure occur when one of the main branches of a renal artery is ligated so long as the rest of the kidney substance is allowed to remain intact. When, however, the opposite renal artery was ligated, a pronounced rise of pressure promptly occurred. To what extent this rise depends upon increased absorption from products contained in the kidney last ligated, or upon the great reduction of functioning renal substance thereby produced, we can determine only by further experimentation. One would now think that both factors played a part and it is perhaps justifiable to hazard an opinion that any retained substance arising from the dying, renal tissue is slowly excreted by the remaining reduced kidney substance, thus accounting for the tendency of the blood-pressure to return to normal after several weeks. Were it not for the facts that unilateral nephrectomy produces no change in pressure while ligation of a renal artery is attended by a prompt rise, the results of these experiments might be interpreted as due to a retention of some product of normal metabolism not detectable by the usual blood-chemistry methods and the tendency of the pressure to return to normal as the result of better excretion following hypertrophy of the remaining renal tissue which is capable of function. As the situation now stands we are confronted with the fact that, under such experimental conditions, the presence of kidney tissue, which has been deprived of its circulation, has been in each case necessary to produce an increase in arterial tension. Whether or not this is a property peculiar to the kidney or is possessed by other tissues under similar conditions, is quite a separate problem the solution of which will be next attempted.

The experience of other investigators in regard to the amount of kidney tissue necessary to maintain life, the nitrogen metabolism and the urine after reduction of renal substance, will be found in the works of Tuffier,[4] Paoli,[5] Bradford,[6] Bainbridge and Beddard,[7] Pearce,[8] and Pilcher.[9] The great amount of kidney substance which must be removed in order to produce any functional defect under experimental conditions is an outstanding feature stated by these authors. Hypertrophy of the remaining kidney tissue takes place very rapidly.

Pässler and Heineke[10] seem to have been the first to make a systematic study of the blood-pressure after removal of varying amounts of kidney. Unfortunately, they did not possess a method for measuring blood-pressure without anesthesia. Taking the mean pressure by cannulating the femoral artery, they noted increases varying from 15 to 29 mm. Hg. in a series of seven dogs. Over fifty per cent of the total kidney substance was re-

moved in all of these animals and, in several cases, five and six subsequent operations were done, thereby reducing the remaining part to a very small amount. An average hypertrophy of the heart of twenty-nine per cent lends further support to their claims for producing an elevation of blood-pressure. No chemical studies of the blood were done. Janeway,[11,12] using a modified Riva-Rocci apparatus, studied the blood-pressure of dogs after complete removal of one kidney and ligation of one branch of the opposite renal artery. He noted average increases of 13, 33, 38 mm. Hg. respectively in the systolic pressure of three animals. These figures were obtained with considerable difficulty by palpation of a superficial artery of the lower foreleg following compression above by a cuff. Though the actual, normal pressures of these dogs (90, 110, 117 mm. Hg.) seem much too low, the change after operation appears to have been clear. Backman,[13] with a Trendelenberg tonometer, was unable to detect any changes in systolic pressure in cats upon which bilateral nephrectomy had been performed. However, upon removal of one kidney and a small piece of the opposite one, an average elevation of 18 mm. Hg. was noted.

Though the methods for estimating blood-pressure used by Pässler and Heineke, Janeway, and Backman are subject to adverse criticism in regard to accuracy, it is, however, highly probable that it was possible to demonstrate a change of pressure by means of them. Attention is again called to the fact that these observers noted an increase of pressure only when some amount of necrotic kidney tissue was undergoing absorption within the body; they did not, however, mention this fact as one of the possible, etiological factors concerned in the production of such a change.

From the present series of experiments it is, however, not yet clear exactly what function the necrotic renal tissue, which is left behind, has in the production of the increased arterial tension but the suggestion that it plays an important part is quite striking. In our present state of knowledge such an opinion is forced upon one by a comparison of the results of reductions of renal substance of fifty per cent by excision of one kidney and by obstructing the arterial blood supply of one kidney and allowing it to remain *in situ*. In the first case, as will be seen by the following table, no increase in blood-pressure has occurred, while in those cases where the kidney, removed from function, was left in place, a marked increase in arterial tension has always followed. So far, no exceptions have occurred to the rule.

Total renal substance reduced fifty per cent.

	Change in blood-pressure	
	Systolic	Diastolic
(A)—By excision of one kidney.		
Experiment 5, Dog 22.....	−11	+1
Experiment 6, Dog 25.....	−13	−16
(Not included in these experiments.) Dog 34.....	−1	+4
(B)—By obstructing arterial blood supply to one kidney, which was allowed to remain in place.		
Experiment 3, Dog 16.....	+16	+22
Experiment 7, Dog 26.....	+47	+55
Experiment 8, Dog 27.....	+27	+43

The difference shown by these two groups of experiments may be more apparent than real since their number is small but, as they stand, one cannot escape the impression that the necrotic renal tissue is an important factor in the production of the rise in blood-pressure. A more accurate knowledge of its status in this respect is anticipated from experiments now in progress.

There is a multitude of valid objections to any theory attempting the explanation of human, arterial hypertension such as could be formulated from this series of experiments and, consequently, none is offered. It is earnestly hoped, however, that, with at least some of the factors in hand for producing experimentally one of the principal characteristics of cardio-renal-vascular disease, further experimentation along these lines will bring us nearer a better conception of this much confused subject.

The chemical studies of the blood were made by Dr. R. R. Hannon, Miss Ruth Loveland, and Mr. David Rioch. I wish to acknowledge my sincere appreciation of their work.

CONCLUSIONS

1. Reduction of renal tissue by excision and by the ligation of renal vessels has been followed, under certain conditions, in most cases, by a rise of both systolic and diastolic blood-pressure and in all cases by a rise of diastolic pressure averaging about 27 mm. Hg.

2. The conditions under which this change has occurred are:

   a—that the total kidney substance be reduced at least fifty per cent;

   b—that, in addition, a portion of kidney which has been deprived of its circulation be allowed to remain *in situ*.

3. Extensive necrosis of renal tissue alone, such as produced by widespread, bland, infarction of one kidney, or the ligation of one branch of a renal artery, has not

proven sufficient, so far, to cause any rise of blood-pressure. Complete excision of one kidney has also been unaccompanied by such a change.

4. The increase in arterial tension reaches its height within a few days following the completion of the operative procedures, after which time it tends to return to normal. The rapidity with which the change occurs seems to be roughly proportional to the amount of functioning renal tissue remaining.

5. After reduction of total kidney substance varying from twenty-five to eighty-five per cent there has occurred no appreciable change in the amount of nonprotein nitrogen or total chlorides of the blood. Where the reduction has exceeded fifty per cent there has always been observed an impairment of the animal's ability to excrete phenolsulphonephthalein.

6. No constant changes have occurred in the volume of circulating blood as shown by the "brilliant vital red method."

Oedema has never been produced in these experiments.

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A COMPARISON OF THE EFFECTS OF GERMANIUM DIOXIDE AND OF SODIUM GERMANATE ON THE BLOOD OF THE ALBINO RAT*

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The recent studies which have been made on the physiological action of germanium dioxide in alkaline solution have demonstrated the fact that it is relatively non-toxic and non-corrosive to the tissues of the albino rat when injected subcutaneously.[1] Following the injection of this compound there is a marked increase in the number of erythrocytes in the circulating blood without the appearance of any nucleated red corpuscles.[2] That this polycythemia is not due to a concentration of the blood-plasma has been shown in another paper.[3] Another study has shown that an increase in the number of nucleated red cells in the bone-marrow follows the injection of this substance.[4]

In the preceding experiments tenth-normal sodium hydroxide was added to the germanium dioxide in order to hasten the solution of the latter. When an attempt was made to repeat these experiments, using a fresh solution of germanium dioxide made up in distilled water without the addition of any alkali, it was noted that the results obtained did not check with those of the previous experiments. It seemed advisable, therefore, to make a study of the relative effects of the administration of the dioxide in neutral solution and in a solution which had first been made alkaline.

Germanium is an amphoteric element and can exist either as the cation or in the anion. The addition of a strong alkali to a solution of the dioxide brings about the formation of the germanate according to the reaction:

$$GeO_2+2NaOH=Na_2GeO_3+H_2O.$$

Another method of preparing sodium germanate is by fusing the dry dioxide with an excess of sodium carbonate in a platinum crucible. The reaction involved is as follows:

$$GeO_2+Na_2CO_3\rightarrow Na_2GeO_3+CO_2.$$

The purpose of this experiment was to determine the relative effects of a solution of germanium dioxide in distilled water, and of a solution of sodium germanate on the erythrocyte count and the hemoglobin concentration of the albino rat.

* Received for publication, March 14, 1924.

EXPERIMENTAL

A sterile 0.4 per cent solution of germanium dioxide was prepared by dissolving one gram of the chemically pure dioxide in an excess of distilled water and then boiling down to a volume of 250 milliliters.

Two solutions of sodium germanate were prepared according to the methods outlined above. Solution "A," a 0.7 per cent solution of the germanate was prepared by dissolving one gram of the dioxide in 250 milliliters of distilled water, bringing about rapid solution by the addition of several milliliters of normal sodium hydroxide. The excess of alkali was neutralized by adding normal hydrochloric acid drop by drop until a pH of 7.0 was obtained. The solution was then sterilized by boiling until the volume was again 250 milliliters.

Solution "B," a 1.7 per cent solution of sodium germanate, was prepared by fusing together in a platinum crucible, one-half gram of germanium dioxide and one and one-quarter grams of sodium carbonate. The fused mass was dissolved in distilled water and the volume made up to fifty milliliters. This solution was sterilized by boiling.

Three series of albino rats were selected for the experiment. Each series consisted of ten animals, five males and five females. Two preliminary red cell counts and hemoglobin estimations, made one week apart, were done on the rats of all three series. Immediately after the second set of determinations had been made, the rats of the first series were injected subcutaneously with 10 milligrams of germanium dioxide per kilo of body weight, and those of the second and third series were injected with 17 milligrams of sodium germanate per kilo of body weight. The amount of germanium as element, (7 milligrams per kilo) was the same for the rats of all three series. One week after the injection had been made, the red cells and hemoglobin were determined again on all the rats.

The samples of blood for the various determinations were taken in each instance from the tip of the animal's tail. These samples were drawn and the germanium compound was injected while the rat was under a light ether anaesthesia. The animals used in the experiment were very tame and accustomed to being handled, and went under the influence of the anaesthetic with but slight symptoms of excitement. By rendering them unconscious, the effect of emotional stimuli, if any, was reduced to a minimum. Lamson [5] has shown that such stimuli cause marked changes in the erythrocyte counts of experimental animals.

In making the red cell counts a standardized diluting pipette and a counting chamber with Neubauer ruling were used. For the hemoglobin estimations we employed a Sahli hemoglobinometer, standardized to read 100 per cent with a hemoglobin concentration of 13.8 grams per 100 cubic centimeters of blood.

RESULTS

The results are summarized in the tables.

Table I shows the effect of the injection of the first solution of sodium germanate, (solution "A"), prepared by adding sodium hydroxide to the solution of germanium dioxide. In this experiment the results are consistent with those of our previous experiments. In the case of every rat which was injected with this solution, there occurred a marked rise in the erythrocyte count and a slight increase in the concentration of the hemoglobin.

Table II shows the effect of the injection of the second solution of sodium germanate, (solution "B"), prepared by the fusion of the dioxide with sodium carbonate. This solution was more concentrated than the previous germanate solution and contained an excess of sodium carbonate. There was considerable inflammation of the tissues at the site of the injection of this solution. In two of the animals this tissue reaction was very severe, and it is interesting to note that in these particular animals there was no increase in the number of red cells following the injection. The remainder of the rats of this series showed marked rises in the red cell counts and increases in the per cent of hemoglobin.

Table III gives the results of the injection of the neutral solution of germanium dioxide. An inspection of this table shows that in this lot of animals there took place no significant rise either in the red cell count or in the per cent of hemoglobin. The maximal fluctuation in this series was less than half a million cells rise or fall. The mean change was 50,000 cells, which is less than the probable error of the mean of this series. Changes in the hemoglobin in this series are all within the limits of accuracy of a Sahli determination.

The results of this experiment show clearly that germanium dioxide in neutral solution is not an effective agent for the production of an experimental polycythemia. That a solution of sodium germanate will produce a marked erythropoiesis, when injected subcutaneously, is shown by the results of Tables I and II. The favorable results of our previous experiments were probably due to the fact that sufficient alkali was added to the germanium dioxide to convert it into sodium germanate. At this time the effect of the alkali was not understood, and the erythropoiesis was attributed to the effect of the dioxide itself.

The exact hydrogen-ion concentration necessary to convert germanium dioxide into sodium germanate has not been definitely determined. Sufficient alkali was added in preparing the first solution of the germanate to obtain a pH of 9.5. In view of the results shown in Table III, it is apparent that the blood and tissue fluids are not sufficiently alkaline to permit this change to take place. Attempts to bring about an increase in the red cell count by the injection of a solution of the dioxide in distilled water, which had been brought to a pH of 7.4

by the addition of sodium hydroxide, were also unsuccessful.

Muller and Iszard [6] have reported rises in the red cell counts of guinea-pigs following the injection of germanium dioxide in neutral solution. They also report similar results in dogs and man. In this laboratory both sodium germanate and germanium dioxide have been tried on a small series of dogs. The effect of the injection of the dioxide was negative, as no increase in the red cell counts occurred. The sodium germanate solution was injected into two dogs and there followed rises of 0.8 and 1.0 million cells respectively.

TABLE I.

Effect of sodium germanate, (solution "A"), on the erythrocyte count and hemoglobin concentration

Rat No.		Preliminary determinations			One week after injection		
		Weight in grams	Hemoglobin per cent	R. B. C., millions	Weight in grams	Hemoglobin per cent	R. B. C., millions
1	a.	153	75	7.63	166	86	9.88
	b.	157	75	7.54			
2.	a.	260	88	9.00	275	90	10.14
	b.	263	86	9.11			
3.	a.	214	73	7.31	234	78	8.67
	b.	220	72	7.12			
4.	a.	260	76	8.60	259	80	9.78
	b.	252	72	8.14			
5.	a.	298	78	7.88	300	86	9.18
	b.	300	75	8.06			
6.	a.	182	86	7.84	184	90	9.17
	b.	180	85	7.94			
7.	a.	214	80	7.67	228	85	8.94
	b.	217	79	7.58			
8.	a.	210	75	7.34	217	85	9.58
	b.	214	75	7.32			
9.	a.	187	85	9.11	194	88	9.72
	b.	191	83	9.02			
10.	a.	174	80	7.61	185	88	8.94
	b.	178	80	7.74			
Mean.	a.	215	79	8.00	224	86	9.40
	b.	217	78	7.96			

Determinations "a" and "b" were made one week apart.

The sodium germanate solution was injected immediately after taking the sample of blood for determination "b."

TABLE II.

Effect of sodium germanate (solution "B"), on the erythrocyte count and hemoglobin concentration

Rat No.		Preliminary determinations			One week after injection		
		Weight in grams	Hemoglobin per cent	R. B. C., millions	Weight in grams	Hemoglobin per cent	R. B. C., millions
1.	a.	178	85	8.26	178	110	10.58
	b.	178	83	8.36			
2.	a.	207	85	8.66	218	105	11.43
	b.	214	80	8.50			
3.	a.	197	82	8.98	187	96	*8.98
	b.	200	80	8.80			
4.	a.	152	75	9.23	154	90	11.42
	b.	155	78	9.31			
5.	a.	162	90	9.27	166	105	11.43
	b.	163	88	9.18			
6.	a.	181	70	8.05	186	90	9.86
	b.	192	75	7.93			
7.	a.	163	80	8.87	164	85	*9.08
	b.	157	88	8.96			
8.	a.	164	84	9.34	179	95	10.27
	b.	168	83	9.23			
9.	a.	148	85	8.20	174	95	9.23
	b.	163	85	8.30			
10.	a.	156	90	8.31	169	95	9.52
	b.	157	90	8.24			
Mean.	a.	171	83	8.72	177	97	10.18
	b.	175	83	8.68			

Determinations "a" and "b" were made one week apart.

The sodium germanate solution was injected immediately after taking the sample of blood for determination "b."

* This animal showed a severe tissue reaction.

TABLE III.

Effect of germanium dioxide on the erythrocyte count and hemoglobin concentration

Rat No.		Preliminary determinations			One week after injection		
		Weight in grams	Hemoglobin per cent	R. B. C., millions	Weight in grams	Hemoglobin per cent	R. B. C., millions
1.	a.	234	80	7.89	240	80	8.00
	b.	237	78	7.92			
2.	a.	180	85	7.87	190	85	8.06
	b.	183	85	7.77			
3.	a.	194	76	9.26	201	75	9.22
	b.	198	75	9.45			
4.	a.	176	90	8.87	185	92	9.07
	b.	181	93	8.94			
5.	a.	201	82	8.44	204	80	8.98
	b.	204	83	8.54			
6.	a.	162	84	7.71	167	85	7.89
	b.	164	85	7.84			
7.	a.	164	82	8.94	165	85	9.06
	b.	163	85	9.11			
8.	a.	234	85	7.30	227	84	7.81
	b.	237	85	7.46			
9.	a.	219	84	8.08	216	88	7.92
	b.	220	85	7.92			
10.	a.	179	85	8.89	187	88	9.27
	b.	182	90	9.07			
Mean.	a.	194	83	8.33	198	84	8.44
	b.	197	83	8.39			

Determinations "a" and "b" were made one week apart.

The germanium dioxide was injected immediately after taking the sample of blood for determination "b."

SUMMARY AND CONCLUSIONS

Three lots of ten mature rats each were injected with single doses of sodium germanate or germanium dioxide solutions. The animals of the first and second series received 17 milligrams of sodium germanate per kilo of body weight. Those of the third series were given 10 milligrams of germanium dioxide per kilo of body weight. The amount of germanium as element was in all cases the same.

Control red cell counts and hemoglobin estimations had previously been made, and one week after the injections a final erythrocyte count and hemoglobin determination were made on each animal and the effect of the injections noted.

It was found that the rats which had received injections of the sodium germanate solutions showed a marked increase in the red cell counts and a slight increase in the percentage of hemoglobin.

The rats which had been injected with the germanium dioxide solution showed little or no change in the erythrocyte counts and hemoglobin readings.

The conclusions drawn from this experiment, therefore, are:

1. That germanium dioxide in neutral solution has no value as an erythropoietic agent.

2. That a solution of sodium germanate is an effective means for the production of an experimental polycythemia.

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HOFBAUER CELLS (CLASMATOCYTES) OF THE HUMAN CHORIONIC VILLUS

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The presence of numerous Hofbauer cells in the stroma of the human chorionic villus has been associated by some authors with degenerative changes in the mesenchyme of the villi, more especially with hydatiform degeneration. Since the history and significance of these cells has recently been discussed by Meyer (1921), it is unnecessary here to review the literature on the subject other than to mention that these cells were recognized long before Hofbauer described them in 1905 as being similar to the wandering cells found in the body.

An examination of fresh and fixed normal villi indicates that the Hofbauer cells are, in reality, more numerous here than in the villi showing hydatiform degeneration. The fresh villi, after immersion in Locke solution with neutral red, are especially favorable objects for the demonstration of the Hofbauer cells. Their general appearance and marked affinity for neutral red reveal their probable identity with the clasmatocytes so abundantly present in various tissues of mammals and birds, both embryonic and adult.

As my interest was first aroused by the remarkable picture presented by these cells in the fresh living villi treated with neutral red, I shall present my findings from this material first. During the past year or two I have examined fresh villi from nine human specimens, varying in age from 6½ to about 17 weeks, and from several full-term placentae. For this material we are indebted to the kindness of Dr. Williams and Dr. Hunner of the Johns Hopkins Medical School. The fetuses were all normal and had been removed, either with the uterus or by Caesarian section, on account of the condition of the mother.

FRESH VILLI

The villi, which were received immediately after the operation, were cut up into small fragments in a dish containing Locke solution with neutral red (about 1-5000). It was found that the various types of cells in the villi, with the possible exception of the syncytial layer, will live for several hours or more at ordinary room temperature. Within a few minutes the neutral red penetrates into the interior of the villus, as witnessed by its accumulation in the numerous vacuoles of the Hofbauer cells, so that the latter stand out very conspicuously in the ordinary coverglass preparations made by mounting a few fragments of villi, in a drop of the neutral red Locke solution, between coverglass and slide. The first preparations usually show no other traces of neutral red in the

villi, except at times a diffuse pink staining of the syncytial layer. Preparations made after the villi have been standing in the neutral red solution for about thirty minutes or more usually show, in addition to the conspicuous accumulation of neutral red in the Hofbauer cells and the diffuse pink staining of the syncytial layer, clusters of red granules or small vacuoles in the epithelial cells of Langhans (Figs. 1, 5), in the mesenchyme cells (Fig. 1), in the endothelial cells, in the white blood cells, and a few in some of the red blood cells. The accumulation of the neutral red is always much more abundant in the Hofbauer cells than in the other types. Since the latter (epithelial, mesenchymal, endothelial, etc.) do not show red granules and vacuoles when the preparations are first made, it seems very probable that these bodies develop after the tissue is immersed in the neutral-red solution. This gradual accumulation of granules and vacuoles which have such a marked affinity for neutral red is not due to the dye, however, since they accumulate also in plain Locke solution, but to an abnormal environment where the oxygen and food supply and the paths for the elimination of waste products are cut off. They are undoubtedly similar to the granules and vacuoles that accumulate in the various types of degenerating cells in tissue cultures (Lewis, 1919) and in most types of cells after death of the animal (Lewis and McCoy, 1922).

That the granules and vacuoles are already present in the Hofbauer cells as soon as the specimens are received can be readily seen by immediate examination without treatment with neutral red. It is quite easy to recognize the unstained Hofbauer cells in spreads of fresh villi. Since these cells appear as highly vacuolated on the first examination as after an hour or two, it seems probable that they are in this condition when normally situated in the uterus.

The reaction of the syncytial layer to the neutral red Locke solution was strikingly different from that of the various other cells. The syncytial layer always contained many minute fat globules, but never any granules or vacuoles with an affinity for neutral red, even after several hours. On the contrary, this layer often took on a diffuse pink tint such as we are accustomed to associate with the staining of dead cells. It would be rather surprising if, on further investigation, the syncytial layer proved to be the least viable of all the villous tissues, as the natural supposition would be the contrary. I have made several attempts to cultivate the syncytial layer in tissue cultures without success. The clasmatocytes and connective-tissue cells, on the other hand, exhibited migration.

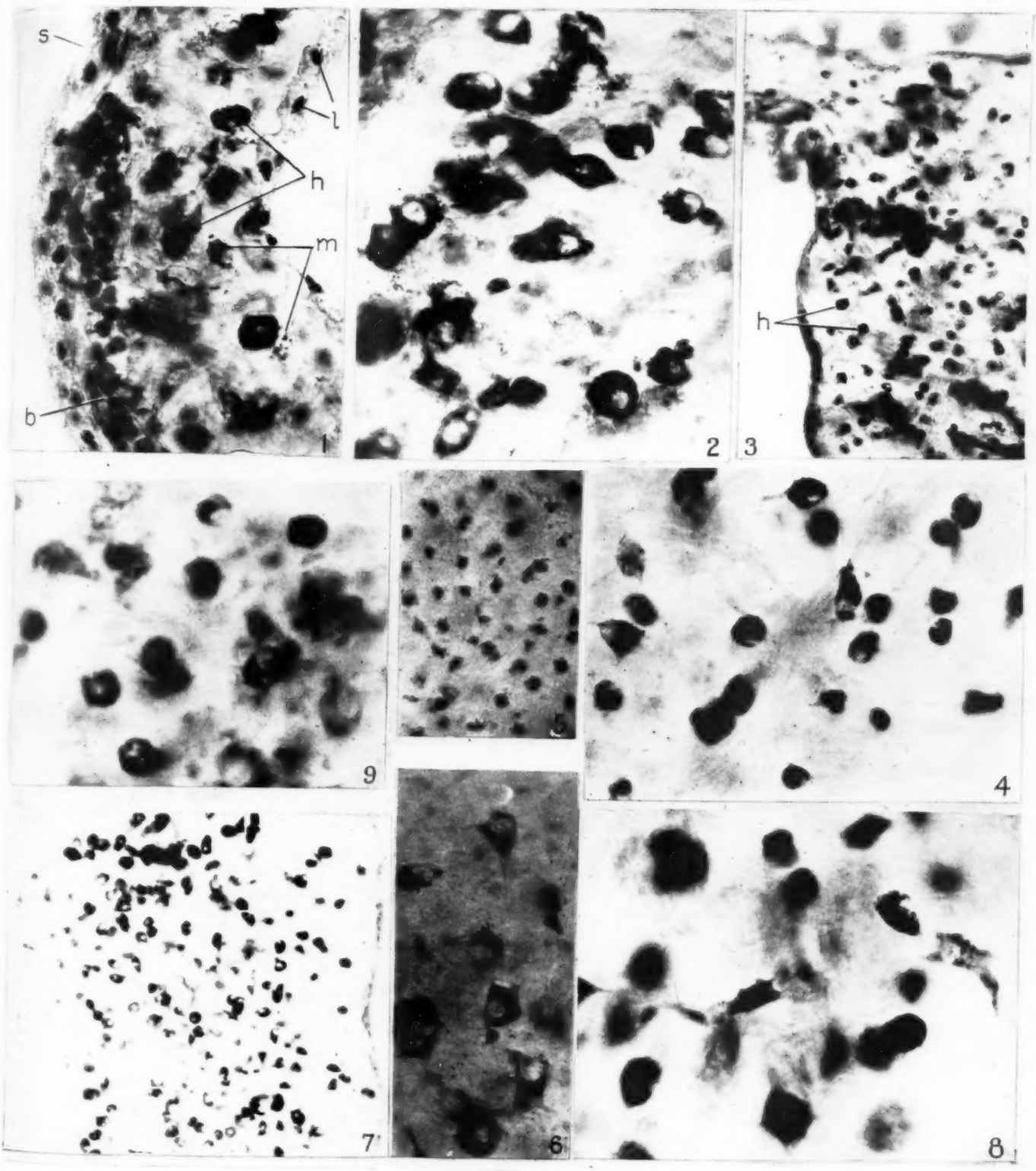
In the youngest fresh villi examined (embryo measuring 14 mm. in length, estimated age 6½ weeks) the Hofbauer cells were numerous and there were indications of transition stages between them and the reticular stroma cells.

A similar condition was found in older villi (embryo 18 mm., estimated age 7 weeks; 29.5 mm. embryo, estimated age 8-6/7 weeks—Figs. 7, 8). The villi contained many Hofbauer cells of various sizes, more or less crowded with neutral-red vacuoles. Some of the Hofbauer cells were large and oval, others small and more or less round. In the larger ones the vacuoles were more numerous and crowded together. In these young stages there were more cells that appeared to be transitional between mesenchyme and Hofbauer cells than in any of the villi from the later stages. Hofbauer cells were equally abundant in the villi from 48 mm. embryos (estimated age about 11 weeks—Figs. 1, 2, 3, 4, 5, 6). Here as in the earlier embryos there was considerable variation in size, form, and neutral-red content, but there were not as many stellate forms. The villi from still older stages, 58 mm. (Fig. 9), 66 mm., and 128 mm. (estimated ages of 11-5/7 weeks, 12-2/7 weeks, and 16-5/7 weeks) presented much the same condition.

The Hofbauer cells in all these villi were scattered throughout the stroma in the large spaces between the reticular mesenchyme cells. They are not to be distinguished from the clasmatocytes so common in adult and embryonic tissues. No especial relation was observed either to the blood vessels or Langhans layer, but they seem to be more or less evenly scattered throughout the stroma, usually a distance of from one to three cells apart.

Our specimens gave no very clear indication of the origin of the Hofbauer cells. Transition-like forms between them and the mesenchyme cells suggest the latter as a possible source of origin. On the other hand, the variation in size of the round and oval ones, down almost to the size of white blood cells, suggests the possibility that they may arise from white blood cells that have wandered into the tissue spaces. Recent unpublished observations of Mrs. Lewis, on the transformation of leucocytes of the human blood into clasmatocyte-like cells in hanging-drop cultures of blood, support such a view. We saw no indication of an origin from either Langhans layer or endothelium. The possibility of their origin from endothelium cannot, however, be denied, as the observations of Sabin (1921) indicate that they may arise from this tissue. From our present knowledge of the subject, it is not impossible to conceive of the clasmatocytes as arising from several sources.

The villi from the full-term placentae seem to contain relatively fewer Hofbauer cells than those from the younger stages. Here they are not very conspicuous, though they contain numerous vacuoles which take up the neutral red. They are more or less elongated in form and lie between the blood vessels and Langhans layer.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FIXED MATERIAL

An examination of the fixed material of the Carnegie collection failed to reveal Hofbauer cells in the villi from the early stages, 2, 3, and 5 mm. embryos (Nos. 2795, 2053, and 4046). In specimens slightly older, 5.2 mm. and 5.5 mm. embryos (Nos. 2813 and 3960) the villi showed a few vacuolated Hofbauer cells scattered in the mesenchyme. They evidently increase rapidly in number, for at 6.7 mm. to 8 mm. (Nos. 3950 and 3441) they were abundant and vacuolated. They continued abundant until the fetus reached a crown-rump length of 204 mm. A few could be recognized up to 260 mm., while in older stages (317 mm. and 330 mm.) none were to be seen. This does not necessarily mean that none were present, however, as the conditions in fixed material are not always favorable for their recognition. Some of the fixed material from villi of younger specimens seemed to contain but few Hofbauer cells, but since the normal fresh villi of corresponding ages, treated with neutral red, contained them in abundance, it seems probable that the discrepancy is to be explained by the condition of the tissue at the time of fixation, poor fixation, or poor staining.

In addition to the material of the Carnegie collection, I have had an opportunity to examine some of the fixed material from the obstetrical department of the Johns Hopkins Hospital. With one exception, the villi from all specimens from six to twenty weeks old contained a fairly abundant supply of Hofbauer cells. These cells were also fairly abundant in the full-term villi.

HYDATIFORM VILLI

I examined fourteen specimens of villi from the Carnegie collection, supposed to show hydatiform degeneration, and did not find that the Hofbauer cells were any more abundant under this condition than in the normal villi, but their distribution was more variable. Some villi seemed to lack them entirely, while neighboring villi contained them in abundance or in varying numbers; compact groups were rarely seen. Meyer (1921) states that the Hofbauer cells are not necessarily pathogenic for hydatiform degeneration, and my observations seem to confirm this view.

FUNCTION OF THE HOFBAUER CELLS

If our surmise that Hofbauer cells are clasmatocytes be correct, and I see no reason to doubt it, these cells probably have a function similar to those so liberally scattered through the body, both of embryo and adult. Here their phagocytic character has long been recognized, hence the name *macrophage*. In tissue cultures this cell type shows a marked ability for the ingestion and digestion of bacteria and various foreign bodies, such as red blood cells, cellular débris, etc. In the villus they probably clear up the tissue spaces of escaped blood cells and other dead material, and perhaps also guard the fetus from bacterial invasion from the mother.

EXPLANATION OF FIGURES

Fig. 1.—Segment of villus, 48 mm. embryo; *h*, Hofbauer cells; *l*, clusters of granules in epithelial cells of Langhans; *m*, mesenchyme cells with granules; *b*, blood vessel; *s*, syncytial layer. ×480.

Fig. 2.—Hofbauer cells in large villus from same specimen as above. ×480.

Fig. 3.—Hofbauer cells (h) from villus, 48.5 mm. embryo. ×146.

Fig. 4.—Hofbauer cells from same villus as above. ×480.

Fig. 5.—Surface view showing clusters of granules in Langhans cells, same specimen as above. ×480.

Fig. 6.—Hofbauer cells from another villus of same specimen as above. ×480.

Fig. 7.—Hofbauer cells from villus, 29.5 mm. embryo. ×146.

Fig. 8.—Hofbauer cells from above. ×480.

Fig. 9.—Hofbauer cells, 58 mm. embryo. ×480.

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THE JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read before the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXV is in progress. The subscription price is $4.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, $5.00 each.

FURTHER OBSERVATIONS ON THE ELEVATION IN BLOOD PRESSURE PRODUCED BY GUANIDINE COMPOUNDS

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and
Walter Stephenson, M. D.

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In a former communication [1] attention was called to the very striking pressor effects of methyl guanidine when administered to dogs intravenously or intramuscularly. The duration of this increased blood pressure is particularly striking, lasting in some animals as long as four and five hours.

We employed methyl guanidine sulphate and methyl guanidine nitrate in the first set of experiments and later we have also worked with guanidine carbonate, guanidine hydrochloride, guanidine thiocyanate, guanidine nitrate, and *as* dimethyl guanidine sulphate. All of these compounds have shown marked pressor effects when injected intravenuosly in doses varying from 0.1 gm. to 0.2 gm. per kilo body weight, the dimethyl guanidine salt appearing to act most strongly, while the guanidine compounds although producing quite as marked an elevation of blood pressure, did not act as promptly as the guanidine salts containing the methyl radicle. These compounds were secured from the Eastman Kodak Company and were injected in a 1% solution dissolved in distilled water. Up to the present forty animals have been the subject of experimentation.

The blood pressure raising effect of the methyl guanidine and dimethyl guanidine salts when injected intravenously is very prompt, a marked rise usually being noted within one minute, often, in fact, before the total dose has been injected. Other profound effects in addition to the rise in blood pressure have been observed.

Immediately following the injection there is a marked retardation of the heart beat accompanied by a great increase in the amplitude of the beats. When a larger dose of .3 gm. to .4 gm. per kilo body weight is administered, these effects are more pronounced, and great variation in the intensity of the individual beats is seen, often accompanied by a marked lowering instead of a rise in blood pressure. A similar prolongation and retardation of the heart beat of the frog after injection of guanidine salts has been described by Burns and Watson.[2]

The effect of the injections of methyl guanidine and dimethyl guanidine salts upon the respiration is also very marked. The respiratory rate is greatly diminished, the animals often showing but four or five respirations per minute. A similar decrease in the respiratory rate following the injection of guanidine and methyl guanidine salts in rats has been described by Klinger.[3] When toxic doses were administered, respiration frequently ceased altogether and artificial respiration became necessary.

After the production of a high blood pressure in several animals the effect of blood pressure lowering drugs was studied. Amyl nitrite pearls were introduced into the rubber tube leading to the dog's trachea and crushed, allowing the animal to breath in the amyl nitrite. This produced an immediate lowering of the blood pressure but only a very transient one, the effect passing off in two to three minutes. A typical tracing of such an experiment is shown in Fig. 1.

Because of the well known effect of calcium salts in combating human tetany and the similarity between this disease and the condition produced by the administration of guanidine compounds, the effect of calcium upon the high blood pressure was studied.

Calcium chloride in a five per cent aqueous solution was employed, the animal being given .1 gm. per kilo of body weight, in five divided doses. The effect of these injections was very marked, the animals showing as a rule a fall to normal of the blood pressure within ten minutes, the blood pressure then remaining normal.

In the first two experiments the entire calcium chloride dose was administered rapidly and the animal's heart promptly stopped beating. We found later, however, that if the doses were divided and each dose administered slowly, two to three minutes being consumed by the injection, the animal lived, although it showed for a time a marked cardiac irregularity (Fig. 2).

The effect of adding equal amounts of potassium chloride to the calcium chloride, was then studied. This combination produced the same lowering of blood pressure without the appearance of marked cardiac irregularities. When this was administered intravenously there was a prompt and permanent fall in blood pressure (Fig. 3). Subcutaneous injection of this compound produced a more gradual but equally lasting fall in the blood pressure to its normal value (Fig. 4).

This permanent fall of blood pressure produced by calcium chloride suggests strongly a definite chemical effect of this substance upon the methyl guanidine responsible for the hypertension as contrasted with the transi-

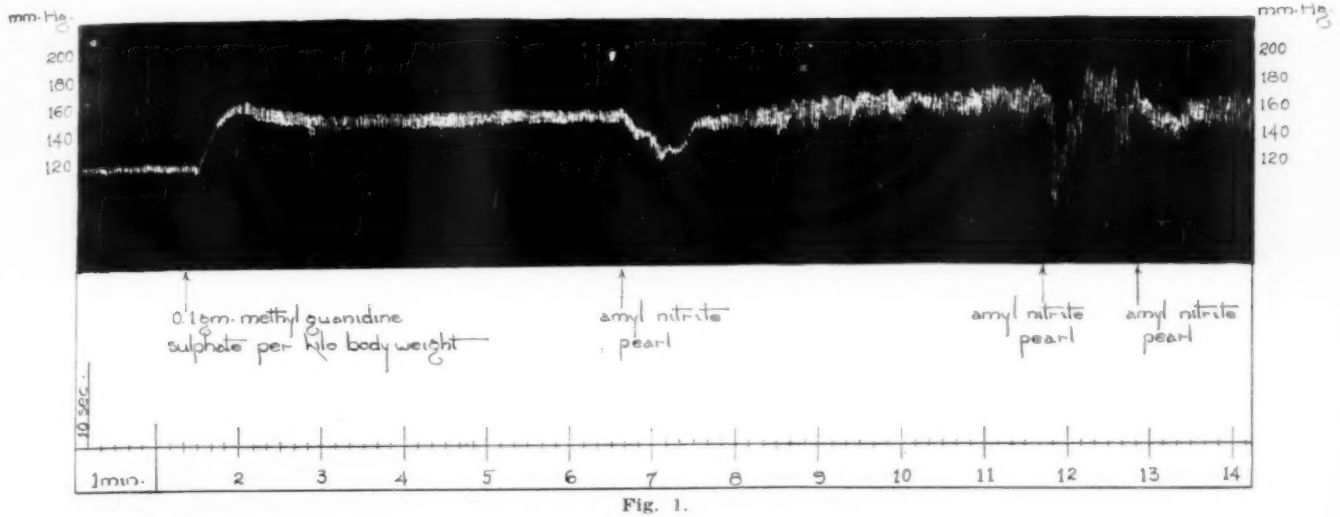


Fig. 1.

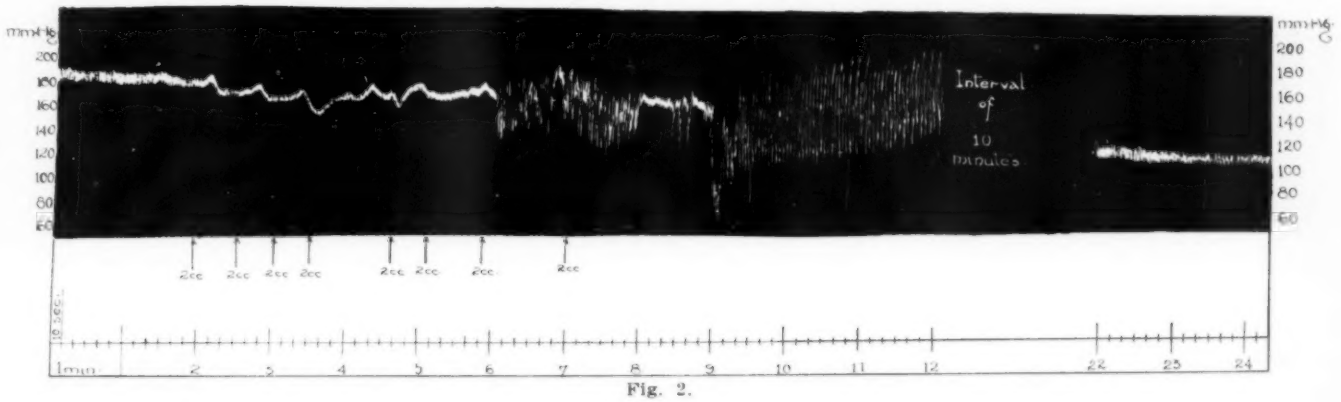
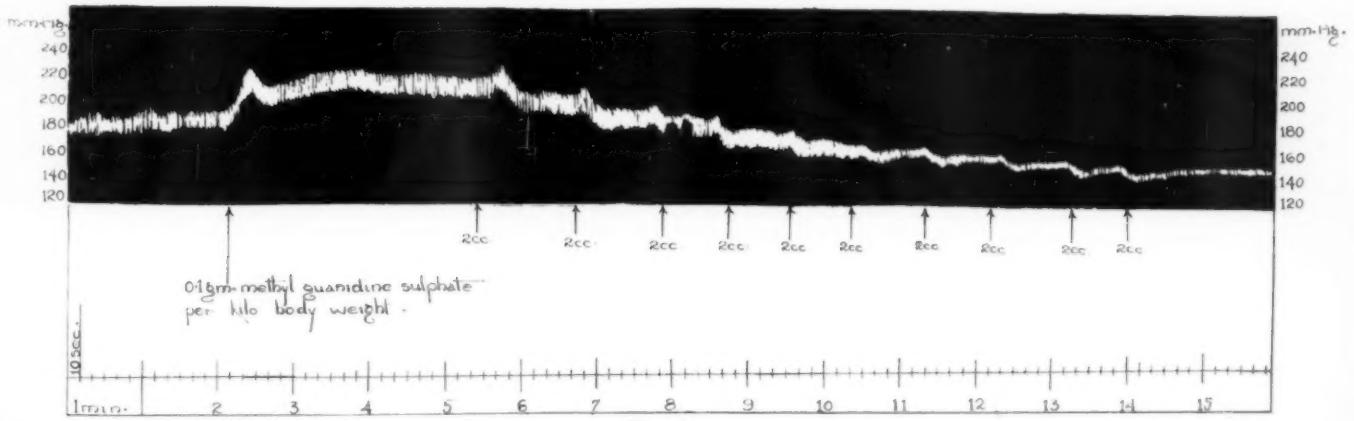


Fig. 2.



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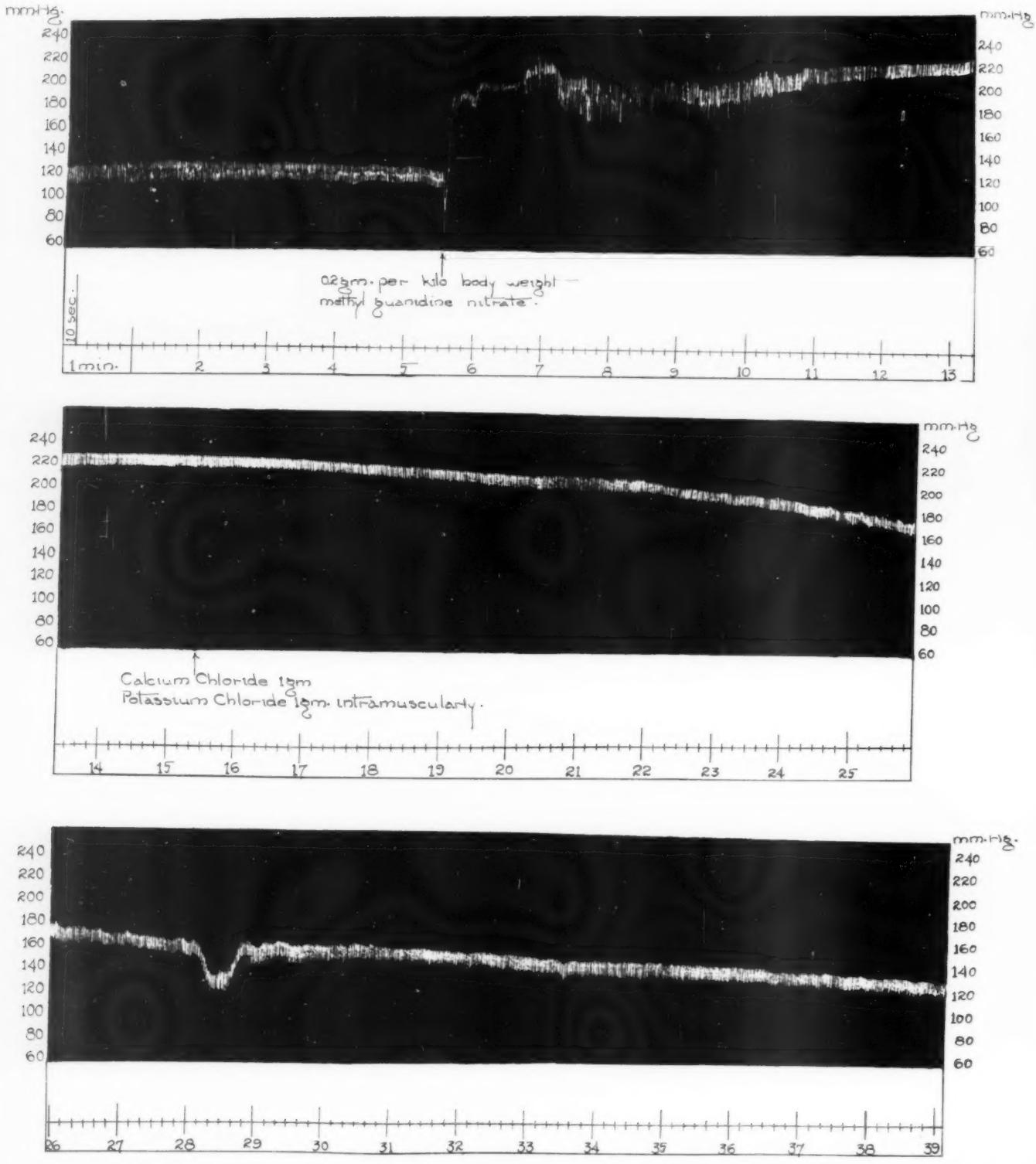
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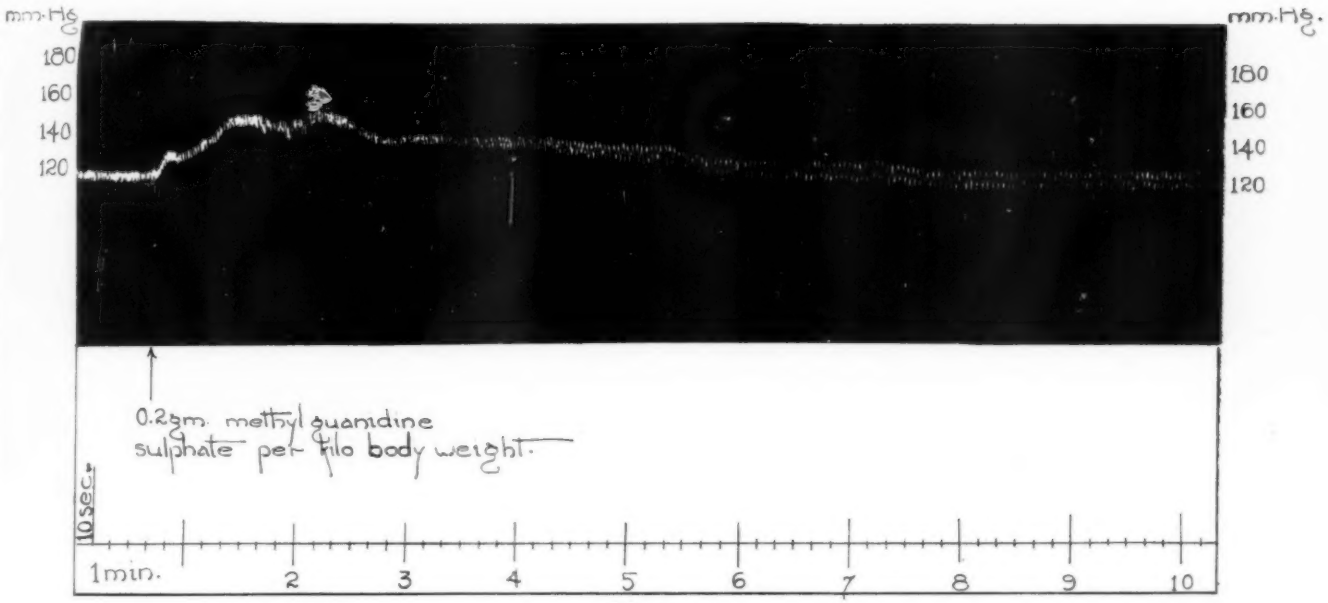
39

Fig. 4.


mm.Hg.
180
160
140
120
mm.Hg.
180
160
140
120
0.2gm. methyl guanidine
sulphate per kilo body weight.
10sec.
1min.
2
3
4
5
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7
8
9
10

Fig. 5.

tory effect produced by a vaso-dilator such as amyl nitrite. We have also found that animals who have been previously injected with a calcium chloride and potassium chloride solution, when injected with methyl guanidine, do not respond with any marked or lasting elevation of blood pressure (Fig. 5). Some additional experiments, which will be reported later, indicate that the elevation of blood pressure produced by guanidine compounds may be abolished by solutions containing no calcium.

CONCLUSIONS

Guanidine, methyl guanidine and dimethyl guanidine salts produce a marked and prolonged rise in blood pressure, accompanied by a slowing of the heart and a decrease in the respiratory rate.

The rise in blood pressure produced by these substances may be promptly abolished by the use of calcium chloride, either alone or combined with potassium chloride.

These experiments prove that substances normally excreted by the urine have a marked and prolonged pressor effect. A further study of the possible relationship between these substances and the high blood pressure of disease may prove of great value.

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LEGENDS

Fig. 1.—Curve showing transient effect of amyl nitrite upon high blood pressure due to methyl guanidine sulphate.

Fig. 2.—Curve showing effect of intravenous injections of calcium chloride upon high blood pressure produced by the injection of methyl guanidine sulphate, .1 gm. per kilo body weight. Note fall in blood pressure, also cardiac irregularity.

Fig. 3.—Curve showing the effect of intravenous injections of calcium chloride and potassium chloride upon hypertension produced by methyl guanidine sulphate.

Dog received two injections of .1 gm. methyl guanidine sulphate per kilo body weight at intervals of ten minutes. Curve shows second injection only.

Note prompt fall in blood pressure following ten injections of 2 c.c. each of the calcium chloride and potassium chloride solution.

Fig. 4.—Curve showing rise in blood pressure produced by methyl guanidine nitrate injected intravenously, and gradual fall in blood pressure following a single intramuscular injection of calcium chloride and potassium chloride. Weight of dog 10 kilos.

Fig. 5.—Curve showing failure of methyl guanidine to produce a sustained rise of blood pressure in a dog injected ten minutes previously with 1 gm. of calcium chloride and 1 gm. of potassium chloride intramuscularly. Weight of dog 10 kilos.

EXPERIMENTAL OBSERVATIONS ON THE ADRENALS AND THE CHROMAFFIN SYSTEM

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INTRODUCTION

Nearly seventy-five years have elapsed since Thomas Addison published his famous monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsule," establishing a disease entity bearing his name, characterized by chronic destruction of the adrenal glands associated with a gradual fall in blood pressure and a peculiar pigmentation of the skin. About fifty years later a brilliant series of investigations led to the second great discovery concerning the adrenal glands—the isolation of epinephrine, an active principle from the medulla of those organs. Epinephrine has proven of tremendous value in the study of the function of the sympathetic nervous system and of smooth muscle. It did not, however, fulfill the promise of becoming a therapeutic agent in Addison's disease. Hence, today, though our knowledge of adrenal physiology has been widened by the isolation and study of an active substance we are apparently no closer to an explanation of the many puzzling aspects of Addison's disease.

Many diseases have gradually yielded their secrets by the experimental reproduction of them in animals upon whom observations can be made and therapeutic procedures attempted which are impossible in the case of man. Therefore, one of the aims in the study of Addison's disease has been the attempt to produce a similar pathological condition in animals. Since Addison's disease in human beings is associated with a gradual destruction of the suprarenal capsules, presumably resulting in a functional insufficiency of those structures, it lay close at hand to try to reproduce the condition in animals by extirpation of the glands.

Numerous have been the attempts to remove the adrenal glands from animals. The results have been fairly con-

stant. After complete removal of both adrenal glands surgically or by cautery, the result has been death almost invariably in the cat and dog within a period of time ranging from twenty-four hours to a week. In the exceptional instances the presence of accessory adrenal bodies or cortical bodies (interrenal substance) which were not removed has nearly always accounted for the survival of the animals. In some animals, however, as for instance in the rat, and to a lesser degree in the rabbit, extirpation of the adrenals is fatal in only a small percentage of the cases. This is due, as has been discovered, to the frequent occurrence in some mammals—in the rat nearly constantly—of accessory adrenal bodies or interrenal substance.

In the dog and cat complete extirpation results, as has been noted, in death within a few days. The symptoms which have been repeatedly observed are gradual weakness and lassitude of the animals accompanied by a rapid terminal fall in blood pressure and body temperature. Occasionally, convulsions have been seen.

These experiments, however, in no way duplicated the picture of Addison's disease. The attempt was then made to produce a more gradual insufficiency, presumably resulting eventually in a gradual exitus of the animal, by extirpating the adrenal glands at several operations but leaving a small fragment.

It was found that removal of one adrenal or one and a half adrenals in the cat or dog caused no symptoms at all and resulted only in the gradual hypertrophy of the portion left in the animal. Biedl,[1] and Crowe and Wislocki [2] then attempted in series of dogs to reduce the adrenals still more. The results of their operations demonstrated that the animals survived without symptoms as long as a fragment of cortex amounting to about one-fifth of the total amount of cortex remained. On the other hand, if more than that was removed, or if the remaining cortical fragment was entirely extirpated, the animals soon died, seldom surviving longer than a week. It became evident that after any attempt at removal one of two things happened, the animals either survived without symptoms or died promptly. A gradual decline of the animals with symptoms resembling those of Addison's disease could not be attained by this method. The chief outcome of this work has been the conclusion that it is the cortex and not the medulla of the adrenal glands which is responsible for the maintenance of life. This conclusion has been substantiated more recently by Lewis and Houssay [3] who scooped out the medulla of the adrenals, leaving only the cortex, with survival of the animals until the latter was removed. Histological check by serial sections showed that the medulla had been completely removed.

Other methods for producing a gradual insufficiency by injecting destructive chemicals or toxic substances directly into the adrenal glands have failed equally in producing the desired effect. However, Marine and Bauman [4] have produced death in rabbits in several weeks after freezing supposedly only the adrenal cortex with an ethyl chloride spray. Their observations are additional proof of the importance of the cortex rather than of the medulla for the maintenance of life. Regardless, however, of whether one does or does not believe that it allows one to distinguish between effects produced by destruction of the cortex alone, their method appears to be dependable for producing an adrenal insufficiency in the rabbit.

One other method requires mention. Hartman and Blatz [5] state that they produced a chronic insufficiency of the adrenal bodies in rabbits by ligating the veins going from them. The animals died after a period of months, but the evidence that death was due to adrenal insufficiency is not convincing. Moreover, Elman and Rothman [12] report the failure of an attempt in cats to duplicate their results. They found that ligation of the adrenal vein of one gland with removal of the other gland resulted either in death of the animals within a week or in indefinite survival with complete restoration of the circulation to the remaining gland, when it was examined, after the animals had been killed several months after operation. If the veins of both glands were ligated, without removal of one gland, an interesting phenomenon was noted. When the animals were killed several months later, one gland was found to have undergone hypertrophy while the opposite one had become atrophic. The atrophy of the one gland on examination proved to be due to a complete disappearance of the cortex with survival of a normal, well vascularized medulla giving the chromaffin reaction. In two animals they demonstrated that if the hypertrophied adrenal was then removed and the atrophied one allowed to remain in, the animals soon died. This observation can well be interpreted as further proof that it is the cortex and not the medulla which is responsible for the survival of an animal.

With the object of securing perhaps a more reliable method of establishing adrenal insufficiency and in the hope of producing a picture in dogs in some measure resembling Addison's disease, we decided to study the effect of the implantation of radium into the adrenal glands. Our results, though far from fulfilling our expectations, may be of interest to those planning similar experiments upon the adrenals or studying the effects of implanted radium upon tissues.*

* A short preliminary account of our experiments was published in the Johns Hopkins Hospital Bulletin (1922).[6] Meanwhile, a note has appeared by Lacassagne and Samssonow (1923) [7] describing briefly a similar attempt to destroy the adrenals in rabbits by the implantation of radium. Three of their rabbits died, one in 5, one in 17, and one in 31 days. At autopsy the adrenals were found completely destroyed. Of another group of five rabbits which received smaller implantations of radium all survived. When they were killed subsequently it was found that the medulla of the adrenals alone had been destroyed while the cortex remained normal.

TECHNIC

Dogs were used in the experiments. Under ether anaesthesia and with sterile precautions a laparotomy was performed on the dog and the adrenals were exposed. As shown in the Table, various procedures were adopted on the adrenals. As a rule one, or one and a half adrenal, was first removed. This was done in order to lessen the amount of adrenal tissue into which it was necessary to implant radium. Moreover, previous observations have shown that removal of as much as one and a half adrenals never resulted in the death of a dog or even in symptoms of insufficiency. Into the remaining adrenal tissue we next implanted one or more glass tubules containing radium emanation.* The glass tubes, measuring in length from 2 to 4 mm., were inserted into the center of the adrenal by means of a hollow 18-gauge needle from which the tube was ejected by means of a wire stylette. The amount of radium implanted varied from 1.7 to 14 millicuries, as may be noted from the Table. The abdomen was then closed.

The method of procedure and the length of survival of the 10 dogs in our series is herewith given:

TABLE

	Amount of adrenal gland left at operation	Amount of radium implanted	Length of survival
1. Dog 19	1/5 of 1 adrenal	1-4.6 mc. point	24 hours
2. Dog 22	1/2 of 1 adrenal	2-1.7 mc. points	24 hours
3. Dog 20	1/2 of 1 adrenal	2-1.7 mc. points	5 days
4. Dog 16	1/2 of 1 adrenal	1-4.6 mc. point	6 days
5. Dog 17	1/2 of 1 adrenal	2-4.6 mc. points	7 days
6. Dog 15	1/2 of 1 adrenal	1-4.6 mc. point	9 days
7. Dog 18	3/4 of 1 adrenal	3-4.6 mc. points	14 days
8. Dog 5	1 entire adrenal	2-2.7 mc. points	16 days
9. Dog 21	1/4 of 1 adrenal	1-1.7 mc. point	21 days
10. Dog 23	1/2 of 1 adrenal	1-1.7 mc. point	32 days

In addition to the 10 animals given in the Table reference is made in the following observations to several dogs (Dogs 2, 3, 4 and 12) which survived the implantation of radium because the adrenals were not completely destroyed. These animals had to be killed.

OBSERVATIONS

On looking at the Table it is seen that the animals survived from 24 hours up to 32 days. From our past experience we believe that all of these dogs except the first would have survived the surgical extirpation of the fraction of their adrenals, if radium had not been simultaneously introduced. Death after more than four or five days, except from subsequent pneumonia is practically unknown to us in dogs which have had as little as one quarter to one half of an adrenal left at operation with no further procedure. In the radium animals shown in the Table death from pneumonia or any other infection has been ruled out by careful examination at autopsy.

Symptomatology.—Clinical observations were made upon the animals from the time of operation until death. The following protocol of Dog 21 illustrates the picture observed in the animals surviving longer than a few days.

PROTOCOL

Dog 21. Mongrel terrier. Male, 4 years. Weight 18 lbs.

Jan. 26, 9.30 A. M.—Ether anaesthesia. Laparotomy. Removal of entire left adrenal. Removal of three-quarters of right adrenal. Insertion of one 1.7 mc. radium into remainder of right adrenal.

4.00 P. M.—Temperature 37.1° C.

Jan. 27.—Slightly depressed and inactive. Appetite poor. Temperature 39° C.

Jan. 30.—Still slightly depressed. Regaining appetite. Temperature 38.8° C.

Feb. 3.—Appears fully returned to health. Active. Appetite good. Temperature 38.7° C.

Feb. 8.—Slightly less active again. Appetite failing. Temperature 38.3° C.

Feb. 11.—Very quiet and inactive. Refuses food. Temperature 38° C. Weight 15¾ lbs. Blood pressure 130/55.

Feb. 12.—Very quiet. Accepts only milk. Blood pressure 115/40.

Feb. 13.—Very quiet. Limbs, nose and skin cool. Slight twitching of facial muscles, also of extremities. Rather easily aroused by noises or quick movements. Gives impression of being jumpy. Temperature 37.5° C. Blood pressure 95/30.

Feb. 14.—Depressed and weak. Refuses food or drink. No diarrhoea. Muscular twitching and sudden jerky movements noted. Reflexes (skin of flanks and knee jerks) very active. Temperature 36.5° C. Blood pressure so low that it can no longer be recorded by the indirect method.

Feb. 15.—Very depressed. Easily excited by noises or movements. Walks about but prefers to sit on haunches or lie down with eyes open observing what is going on. Accepts water only. Temperature 37.1° C. Weight 15⅛ lbs. Blood pressure too low to record. Pulse rapid and feeble. On the evening of this day diarrhoea developed.

Feb. 16.—Quite weak. Makes no attempt to rise. Not unconscious. Diarrhoea has ceased. Pulse very weak. Temperature 34.3° C. Becomes comatose during day. Temperature continues to fall. At 4 P. M. temperature 30.3° C. Animal killed. Survival, 21 days.

The death of all of our animals has been preceded by a terminal fall in temperature, as illustrated in the above protocol, and by a fall in blood pressure in so far as we have had an opportunity to observe it by Kolls' method.† In the animals dying within several days after operation the fall in temperature and blood pressure preceded death,

* The radium used in these experiments was given us by the Howard A. Kelly Hospital.

† We are indebted to Dr. A. C. Kolls for the estimation of the systolic and diastolic blood pressures in this and several other animals by means of an apparatus which he has designed for determining the blood pressure indirectly in the unanesthetized dog. (A. C. Kolls, Journ. Pharm. & Exper. Therap., 1920, XV, 443.)

as a rule, by a few hours only. In the several animals surviving longer than a few days the symptoms have been more gradual, appearing, as a rule, three to four days before death.

Adrenals.—Marked changes were invariably found in the adrenals of the animals which died following implantation or were killed after months when implantation had not caused death. In those which died within several days after operation, the adrenal tissue appeared in the gross to be swollen, soft and hemorrhagic. The color of these adrenals was a splotchy dark red. In animals surviving the first few days, the gross picture changed. In them the adrenal tissue was found nearly always surrounded by adhesions and embedded in scar tissue,—firmer and greater in amount the longer the animals had survived. Because of the adhesions and scar tissue with obliteration of the smooth capsule, the gland tissue was in several animals difficult to see until it was located by sectioning the tissue of the region with a knife. On gross section, however, almost invariably the remains of adrenal tissue could be recognized by finding distinct remnants of a portion of the capsule or of the cortex. As a rule, the adrenal tissue surrounding the implanted glass tubes was caseous looking and friable. In color it was usually whitish or yellow, although irregular, discolored red or brown areas were often visible, indicating recent or old extravasations of blood. Occasionally the cortical remnants appeared as extremely yellow irregular nodules. Small deposits of calcium were frequently encountered by the knife.

The microscopic changes produced in the adrenal tissue by the radium were quite uniform. Around each glass ampoule of radium there was produced invariably a spherical area of completely necrotic tissue with a diameter of eight to ten millimeters (Figs. 1, 3 and 8). Within this sphere of necrotizing influence the epithelial cells of the cortex and medulla were the first elements to undergo change. The nuclei of these cells lost their finer structure and broke up finally into irregular fragments which eventually entirely disappeared. The cytoplasm underwent simultaneous degeneration, characterized in the cells of the medulla by loss of the chromaffin reaction, and in the cortical cells by a disappearance of their finely vacuolated cytoplasmic structure. The changes proceeded rapidly to the complete breaking up of the cell cytoplasm into a finely granular eosin-staining dust-like debris. The connective-tissue framework of the gland seemed to be more resistant to the disintegrative action of the radium. The fibroblasts themselves underwent cell death and gradually faded away. But the supporting framework of closely interwoven reticulum fibers remained unaffected by the rays and it was due to this fact that the microscopic sections frequently exhibited a characteristic appearance (Figs. 2 and 5). One observed, as the final picture of the destruction of the adrenal, this fibrous reticulum containing within its meshes structureless, uniformly eosin-staining, finely granular debris. The connective-tissue meshwork permitted one often to distinguish the capsule, the arcuate trabeculae, characteristic of the zona glomerulosa, and the condensation of fibers separating the cortex from medulla, long after all cellular elements had been destroyed (Fig. 2). The blood-vessels disappeared entirely except for an occasional fibrous skeleton representing the former position of an arteriole or vein. In the area of necrosis, finally, there occurred frequently a deposition of calcium particles either as scattered fine granules over a considerable area or as a few larger clumps. Here and there groups of clefts or narrow slits were observed in the necrotic tissue, the result of the formation of cholesterin crystals.

Surrounding the area of necrosis just described and merging with it was a zone of reaction characterized by injury to the tissue without total necrosis. In this zone the most striking things were the presence of extravasated blood cells, the appearance in places of mononuclear cells or polymorphonuclear leucocytes, and certain changes in the interior of many of the small arteries and veins. The extravasated blood cells, mostly erythrocytes, lay free for the most part in the interstices of the connective tissue. The older extravasates, however, were undergoing resorption, in part, by passage of the blood cells into the regional lymph nodes, and in part also by disintegration *in situ*. The resultant debris lay either perfectly free in the tissue or had been taken up into the cytoplasm of mononuclear cells in which it appeared as greenish-yellow metallic looking pigment.

A number of the smaller arteries and veins in this region were thrombosed (Fig. 8). In others the intima had separated from the vessel walls and lay as a wrinkled structureless membrane within the vessel lumen. Other vessels appeared perfectly normal. In a few animals which were killed several months after implantation of radium the thrombi in the vessels had become partially canalized. No changes were noted in the walls of the neighboring larger vessels, such as the aorta or vena cava.

In several animals changes were observed in organs other than the adrenals. The commonest of these was a degeneration, in several instances amounting to necrosis, of a small part of the liver or of the upper pole of the kidney which lay in contact with the adrenal tissue. Changes in somewhat more remote parts of the kidney and liver were observed in two animals, but detailed reference to them will be reserved until a later paragraph. The retroperitoneal lymph nodes were found enlarged in every instance and on section the sinuses of the nodes were observed to be crowded with red blood cells and with mononuclear cells many of which contained pigment.

In several animals, which failed to die after implantation of radium and were afterwards killed, the adrenals were found to have been only partly destroyed. One

pole of the adrenal tissue as a rule showed healthy cells, usually both cortical and medullary elements. We believe, however, from previous experience and from several of our present experiments, that it is probably the cortex alone which is responsible for the survival of the animal. As an illustration of this, one of our radium experiments will serve. The protocol reads as follows:

PROTOCOL

Dog 4.—Female. Aged 2 years.

Oct. 18.—Ether anesthesia. 1. One 7 millicurie tubule implanted into each pole of right adrenal. 2. Removal of all of left adrenal except a small fragment of cortex at upper pole. Uneventful recovery. No symptoms of adrenal insufficiency.

Dec. 12.—Ether anesthesia. 1. Removal of fragment of cortex left at previous operation at upper pole of left adrenal. Animal slow in regaining consciousness from anaesthesia.

Dec. 13.—Animal died this morning. Section of the fragment removed shows total absence of chromaffin cells but the presence of the zona glomerulosa and part of the zona fasiculata (Fig. 7).

Autopsy.—The right adrenal, when divided by a series of sagittal cuts, reveals numerous whitish looking necrotic areas with here and there red patches resembling hemorrhages. It is thought that in one or two places cortex and medulla can be distinguished. In microscopic sections this adrenal is found to be totally necrotic with no healthy cortical or medullary cells visible anywhere (Fig. 8).

This we believe is an instance of the survival of an animal on a cortical fragment alone after the other adrenal had been destroyed by radium. Several other examples of the survival of animals on cortex alone after the chromaffin system had been almost totally extirpated will be given below.

Abdominal chromaffin body.—In the dogs which died after implantation of radium into the adrenals we have examined the abdominal chromaffin body for the presence or absence of the chromaffin reaction. We have already reported the detail of these observations in another place [6] but the principal finding will be given here again.

It may be recalled that in the dog a band of chromaffin cells about one to two millimeters in width extends almost uninterruptedly from the region of the superior mesenteric artery to the neighborhood of the inferior mesenteric artery. In animals with radium implantations, dying of adrenal insufficiency, these cells gave a conspicuous chromaffin reaction at the time of autopsy. This has been found to be the case not only in animals killed by radium, but also in dogs dying of an insufficiency produced by surgical removal of the adrenal glands alone. As has been outlined in the previous communication, we conclude from the physiological observations of Kahn,[8] Fulk and MacLeod,[9] and others, as well as from the evidence that the abdominal bodies give the chromaffin reaction in animals dying from adrenal insufficiency, that these bodies function and produce a not insignificant quantity of epinephrine. Despite this fact animals die after extirpation of the adrenals.

In view of the fact that animals do not die when the medulla of the adrenal glands is removed, but succumb rapidly when the cortex is extirpated, the question of the relative importance of cortex and medulla for survival is answered. However, the question remains whether or not the remaining chromaffin tissue represented in large measure in the dog by the abdominal chromaffin body plays an important rôle in the maintenance of life after destruction of the medulla. In order to ascertain the effects of destruction of all of the chromaffin tissue in so far as this is possible, we have removed the medulla of the adrenals as well as the abdominal chromaffin body from two dogs, leaving a fragment of cortex intact. Both of these animals survived destruction of the adrenal medulla and removal of the abdominal chromaffin body without symptoms. On eventual removal of the remaining fragments of cortex, at subsequent operations, the animals died, as was expected. There seems little doubt, therefore, that all but a very small fraction of the total chromaffin tissue can be removed in the dog without causing death.

The following protocol illustrates this experiment:

PROTOCOL

Dog 31.—Male. 1½ years.

Jan. 19.—Ether anaesthesia. 1. Removal of entire abdominal chromaffin body. 2. Removal of entire right adrenal. 3. Ligation of adrenal vein distal and proximal to left gland.

Mar. 2.—Ether anaesthesia. 1. Removal of upper pole of left adrenal (about 1/3). Uneventful recovery. No symptoms of adrenal insufficiency.

April 13.—Ether anaesthesia. 1. Removal of lower pole of left adrenal. 2. Medulla of remaining median portion of left adrenal cauterized. Uneventful recovery. No symptoms of adrenal insufficiency. Blood pressure reading at this time 185/90.

May 15.—Ether anaesthesia. 1. The core of remaining adrenal once more cauterized. Uneventful recovery. No symptoms of adrenal insufficiency. Blood pressure reading at this time 180/80.

June 1.—Ether anaesthesia. 1. Removal of fragment of adrenal consisting of cortex only.

June 2.—Blood pressure too low to record by indirect method. Animal apathetic and drowsy.

June 3.—Animal found dead this morning.

Autopsy findings: No trace of adrenal tissue or of the abdominal chromaffin body found. No chromaffin cells are found in the fragment of adrenal removed at last operation (June 1). This fragment consists of cortical tissue only with three well defined layers. The center of the adrenal is composed of scar tissue.

It will be seen that in this animal no symptoms were noted until the last fragment of cortex was removed. Moreover, the animal's behavior and its blood-pressure remained undisturbed until after the final operation. Until that time the animal reacted normally to stimuli of

pain, fear, and pleasure. And while the blood pressure was being taken, it was noted that the pressure rose instantaneously by ten or fifteen millimeters on slight emotional stimulation just as in the normal dog.

These experiments indicate again the importance of the cortex in the maintenance of life and at the same time the relative unimportance of the removal of the medulla besides a great fraction of the remaining chromaffin tissue. It has been claimed recently (Hartman [10]), however, that the cortex, as well as the chromaffin cells produce epinephrine. If this proves to be the case, such a function on the part of the cortex cannot be considered as its sole or principal one. For the experiments of Elman and Rothman, as well as our own, indicate that tissue producing epinephrine, such as the medulla or the abdominal chromaffin body, is in itself incapable of maintaining life after all the cortical substance has been destroyed.

Effect of Radium Implanted into Adrenals upon Other Tissues.—Radium emanation emits α, β and γ rays. The α rays possess little penetrating power, but have a great necrotizing action within a short radius. These rays are responsible for the rather sharply delineated spherical area of necrosis with a diameter no greater than 8 or 10 millimeters surrounding the implanted radium. The β and γ rays, however, are penetrating ones and exert their action over a much greater radius. These latter may be screened out by wrapping the tubules containing the emanation in platinum foil,[7] but in our experiments we have made no attempt to do so.

Certain changes, which we have observed in several of the abdominal organs near the adrenals in two dogs, are possibly due to the penetrating effects of the radium.

In the majority of our animals there is no demonstrable effect of the radium except upon the adrenal tissue into which it was implanted, besides an extension occasionally of the necrosis immediately about the radium to a small portion of the upper pole of the kidney, a lobe of the liver, or the musculature of the diaphragm in immediate contact with the adrenal. In two animals, however, we have noticed changes in the kidney and liver at a distance greater than the ordinary radius of the zone of necrosis. This effect was observed in Dogs 8 and 4 which were killed 45 and 56 days after the implantation of radium. These two animals were the longest to survive of our series. However, they did not receive equal amounts of radium; Dog 8 receiving the relatively small quantity of 2.6 millicuries, while in Dog 4 the large amount of 14 millicuries was deposited in the adrenal.

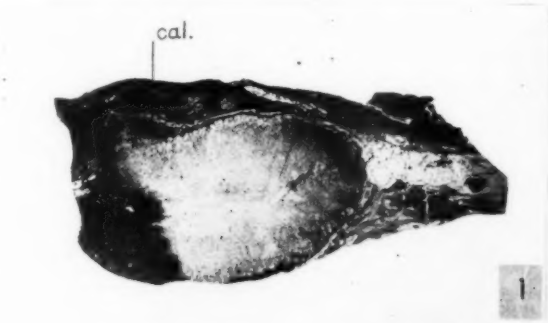
The changes in the kidney and liver consisted of numerous small foci of hemopoiesis. In the kidney these foci were located in the cortex and consisted of groups of cells situated between the convoluted tubules and about the glomeruli. Several glomeruli had undergone partial degeneration by the spread of the hemopoietic process and in one place an atrophic glomerulus had become completely enclosed in an area of cell proliferation. We have studied only haematoxylin and eosin sections of these areas. However, proliferating red blood cells, recognizable as megaloblasts and normoblasts, were seen in large numbers. The two livers differed in appearance. The one, similarly to the kidneys, contained groups of proliferating erythrocytes, in clusters of from four to twenty cells, located in the walls of the sinuses in the periphery of the lobules. The other liver showed much larger masses of cells occupying the stroma about many of the branches of the portal vein and the bile ducts. In this liver, moreover, the cells were in small part proliferating red cells, but chiefly of the white series. Some neutrophilic and eosinophilic myelocytes were identified, but numerous polymorphonuclear eosinophiles and neutrophiles were also present. The bone-marrow in these animals showed no signs of heightened cell formation, indicating that the conditions described were purely local.

We are by no means convinced that radium was responsible for the changes in the liver and kidneys in these two animals. The lesions occurred in only two out of a series of fourteen dogs. However, they occurred in the two individuals which survived longest. Moreover, one animal was subjected to a large dose of radium, the other to a small dose. It must not be forgotten that in the dog such lesions possibly occur spontaneously, though rarely, as the result of infections or other causes. In addition, it may be recalled that stimulation of tissues to blood formation has been obtained by various experimental procedures, such as partial obstruction of the circulation to an organ and by the enteral and parenteral absorption of split proteins. The possibility exists that protein decomposition products liberated from the necrotic adrenal tissue reached the liver or kidney, through the circulation, or by way of lymphatics, eliciting there the changes which we have observed. Kuczynski [11] describes and pictures changes in the liver, after intraperitoneal injections of protein substances, closely resembling those here mentioned.

Lastly, we must make note of the failure to observe any changes in pigmentation in our series of dogs. In several the mucous membrane of the mouth was carefully watched for any increase in pigment, but no augmentation was noticed. In one animal (Dog 21) a zone of skin was shaved encircling the trunk and a belt made of cloth was fitted snugly around the animal's body. No changes in pigmentation developed in the skin beneath this belt or elsewhere.

Summary

1. An adrenal insufficiency was produced in dogs by the combined surgical removal of a part of the adrenal glands and implantation of radium into the remainder.



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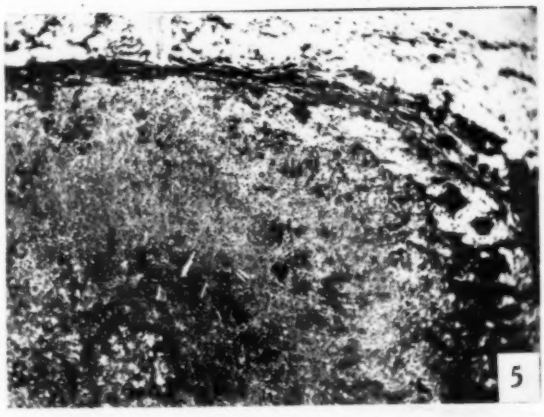

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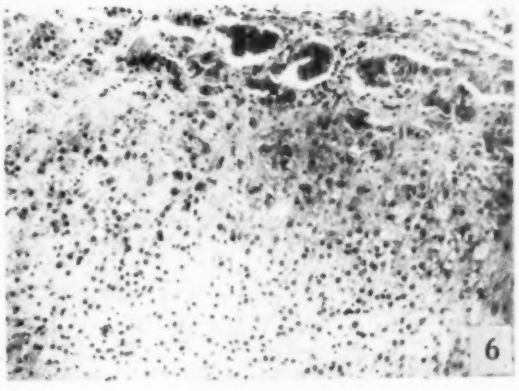

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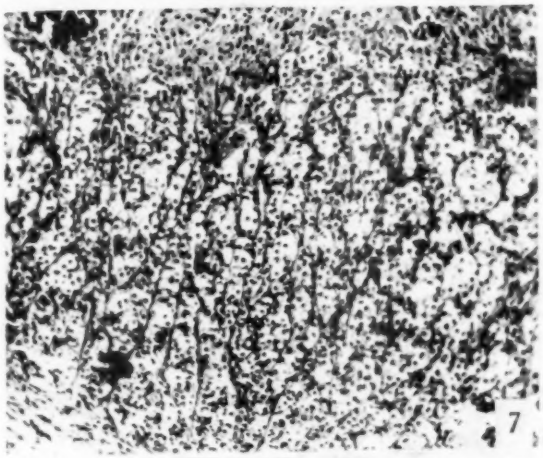

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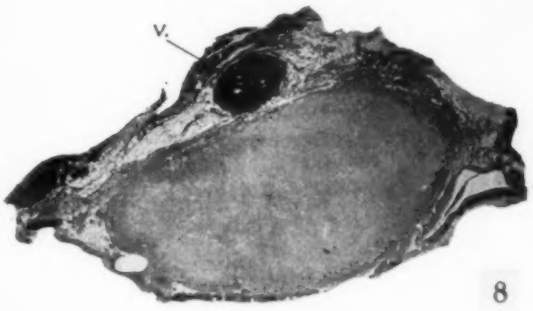

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2. The radium produced an area of necrosis which gradually destroyed the adrenal tissue.

3. The medulla of the adrenals and the abdominal chromaffin body were destroyed in the dog without producing symptoms.

4. A fragment of cortex amounting to about one-fifth of the total cortex was found to be necessary for the maintenance of life. After removal of all the cortex, the animals died with a terminal fall in blood pressure and temperature.

5. If the cortex as well as the chromaffin system produces epinephrine, this fact would not explain the death of animals after extirpation of the cortex.

EXPLANATION OF FIGURES

Fig. 1.—Dog 5. Right adrenal showing total necrosis 16 days after the implantation of two 7 mc. tubules. Cal. Calcium deposit. × 8.

Fig. 2.—Dog 5.—Higher magnification from Fig. 1 showing a portion of the adrenal capsule with the zona glomerulosa and fasciculata beneath it. Note the complete disappearance of cellular elements. × 110.

Fig. 3.—Dog 21. Remainder of right adrenal showing complete necrosis of the gland except for a small area of still recognizable cortical cells, 21 days after implantation of 1.7 mc. tubule. Cor. Cortical cells. × 10.

Fig. 4.—Dog 21. Higher magnification from Fig. 3, showing the small area of disintegrating cortex. × 60.

Fig. 5.—Dog 4. Portion of necrotic right adrenal, 56 days after implantation of two 7 mc. tubules. × 52.

Fig. 6.—Dog 4. Another portion of the same adrenal. × 100.

Fig. 7.—Dog 4. Fragment of healthy cortex remaining at site of left adrenal, upon removal of which the dog died. × 110.

Fig. 8.—Dog 8. Portion of remainder of right adrenal, showing total necrosis 45 days after implantation of one 2.6 mc. tubule of radium. Note thrombosed and partially canalized vessel in capsule. V. Thrombosed blood-vessel. The animal did not die because another portion of this same adrenal possessed healthy cortex. × 12.

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NOTES ON NEW BOOKS

Medical and Veterinary Entomology. By WILLIAM B. HERMS. 2nd Edition, completely revised. *(New York. Macmillan Co., 1923.)*

Those who are familiar with the first edition will find most of its text in the second, but some of it has been recast and there are many valuable additions. The most extensive of these, naturally, occur in the chapter on lice and in the three devoted to disease-bearing mosquitoes and their control. For the most part, the difficult task of fusing together the old text and the new material has been very well performed.

Professor Herms' book is the best illustrated textbook of Medical Entomology that has ever appeared in America, and it has few rivals in this respect anywhere. The subject-matter is well arranged and ease in finding desired information is assured by a full Table of Contents and both author and subject indices.

Its value for either veterinarians or health officers is greatly increased by the attention given to methods of treatment and control. Much of this material comes from the actual experience of the author and some of his students, and this phase of the book will be greatly appreciated by those who are interested mainly in the practical aspects of Medical Entomology.

And, as the title of the volume implies, the subject-matter includes insects of both medical and of veterinary importance. Few texts on Medical Entomology are able altogether to avoid reference to the insect pests of domestic animals, but few have ever attempted, as this one does, to include a full and adequate treatment of Entomology as it affects the veterinarian.

The main faults, as they appear to me, are as follows: First, the various insects and arachnids taken up in the text are treated as isolated groups only. For example, we find chapters or sections on Mosquitoes, Horse-flies, Buffalo Gnats, House-flies, Blood-sucking Muscids and Myiasis, but nowhere any general discussion of the great order Diptera, to which all these forms belong, nor of its larger sub-divisions. This, to my mind, is a grave defect in a book avowedly intended as "a

Textbook for use in Schools and Colleges." In the second place, the volume includes very few keys for the identification of insects, which is a serious omission in a "handbook for the use of Physicians, Veterinarians and Public Health Officers." In practical work, the identification of a disease-carrying insect is all-important. Of what value is the knowledge of control measures if one cannot find and recognize the insect to whom the measures are to be applied? It must be admitted that this fault is neutralized, to a considerable extent, by the profusion of illustrations, which, after all, are of more value than keys to a non-entomological student.

But, to my mind, the greatest fault that one can find with this book lies in its restricted scope. Almost the entire volume deals with insects and arachnids which present a practical problem in the United States, and particularly in the state of California. The reprinting of Howard, Dyar and Knab's key to the anopheline mosquitoes found in North and Central America under the title "Key to the Species of Adult Anopheles Mosquitoes," without any further explanation or restriction, is an accurate index of the way in which Professor Herms dismisses the problems of foreign countries. While this increases the value of his book for workers in the United States, especially on the Pacific Coast, it makes the volume of almost no value to workers in the tropics. And the tropics, after all, are the field where Medical and Veterinary Entomology find their great tasks and the real justification for their existence as separate sciences. F. M. R.

Rhus Dermatitis. By JAMES B. MCNAIR. *(The University of Chicago Press, 1923.)*

The book contains sixteen chapters, giving abstracts of typical cases from the literature, a bibliography and appendix.

There is a most exhaustive account of the botanical features of Rhus toxicodendron, radicans and diversiloba; the origin and occurrence of the poison; a chapter on the liability of poisoning relative to growth of the plant; the nature of the toxin, its chemistry, pathology, and the method of transmission of the poison from plant to person. Other significant features includes the clinical aspects, internal poisoning, immunity and —most interesting—a long list of approximately two hundred and fifty remedies which have been employed up to the present time. The book concludes with a contribution to the chemotherapy of Rhus dermatitis and a tentative method for treatment.

These chapters represent in the main a collection of the author's contributions made from time to time to the literature; and possibly a better arrangement of the topics could have been made. However, they appear to contain practically everything of value known regarding this obnoxious disease of the skin. The author's attempt to open up newer fields of research for finding an adequate remedy must certainly be commended. As a monograph for reference it is unquestionably to be highly recommended, and should command a suitable place in any collection of medical literature. I. R. P.

Blood Chemistry: Colorimetric Methods for the General Practitioner, with Clinical Comments and Dietary Suggestions. By WILLARD J. STONE. $2.25. *(1923, New York, Paul B. Hoeber.)*

In view of the fact that there are already available at least three excellent manuals of blood chemistry, it is difficult to find a compelling necessity for this little book. It is true that its author does attempt to give more ultrapractical clinical interpretations of the chemical findings, but it is doubtful whether the didactic and very positive tone assumed in this respect is entirely justifiable. As far as the description of the chemical methods is concerned, it is felt that even a graver criticism of inaccuracy and incompleteness is to be made. In his effort to simplify the technic to meet the limited training and facilities of the general practitioner the author has gone a bit too far. Thus, for instance, he gives a modified procedure of the Folin-Wu method for the determination of non-protein nitrogen, changing the original details concerning the heating and cooling of the digestion mixture in such a way as to lead most certainly to incomplete oxidation or to the production of an undesirable turbidity or to both. These details were most carefully worked out by Folin and Wu and are strongly emphasized in their original article as being of great importance if accurate results are to be obtained. Similar simplifications and omissions of important details of the other methods given render the book almost worthless as a chemical manual. Furthermore, its scope is much too limited, as will be found by any user of it who, for example, would wish to ascertain the degree of acidosis in his diabetic patient from the determination of the carbon dioxide combining power of the plasma by the very simple and rapid Van Slyke method. For some reason this important method is not given in this text. The appropriateness of the chapter on "Diabetic Management" in a small manual of this kind may also be questioned. W. A. P.

Clinical Periodontia. By PAUL R. STILLMAN, D. D. S., & JOHN O. MCCALL, A. B., D. D. S. *(New York. The Macmillan Company, 1922.)*

The authors deserve a great deal of credit for this pioneer work. It fills a long felt want for the undergraduate student, the general practitioner and the periodontist.

The chapter on the normal and pathological is particularly good and very well illustrated.

The etiology, possibly, is a little profuse, and the traumatic occlusion rather overdone as a factor. It appears that the authors have not overlooked any source, either systemic or local, as being a possible factor in peridental disease.

The nomenclature at times, to any one not a periodontist, is a little new and confusing, but it may, through more constant use, be adopted by the general practitioner; if not, it will have to be revised. Our opinion is, that it should be revised. Dr. D. Noel Patton of the University of Glasgow says: "The physician of the past considered he had made a diagnosis when he was able to give his patient's disease a name." Let us, by all means, go a little farther than names, but when we do use them, let them be intelligible to the average man, and not to a limited few only.

The work as a whole, however, makes a very good textbook for the student, and is a valuable addition to the graduate's library. L. D. C.

Regional Anesthesia. Its Technic and Clinical Application. By GASTON LABAT, M. D., Lecturer on Regional Anesthesia at The New York University, etc. With a foreword by WILLIAM J. MAYO, M. D. $7.00. *(Philadelphia and London. W. B. Saunders Company, 1922.)*

Labat is well qualified to write on regional anaesthesia. He has had a wide experience in France and more recently also in this country, where, in addition to his own operations, he had the opportunity to test the method by anaesthetizing the patients of other surgeons. The aim of his book is to present the methods of regional anaesthesia, which demands a some-

what more exact knowledge and technique than the more simple ones of direct infiltration or infiltration block. He deals with regional anaesthesia of the various segments of the body and discusses each topic from the standpoint of landmarks, technique, and infiltration. Operative procedures are not dwelt upon except as to the general type of operation permissible.

The text includes cranial nerve block and paravertebral block of the spinal nerves. Anaesthesia of the brachial and lumbar plexuses in operations on the extremities and the rôle of splanchnic analgesia in abdominal surgery are described. The possibilities of regional anaesthesia in genito-urinary and rectal surgery are explained. The author discusses at length the methods of, and indications for, intraspinal block or spinal anaesthesia, and concludes the book with a general résumé of the value of regional anaesthesia in the various parts of the body.

Labat presupposes in the reader some knowledge of the scrupulous, meticulous care in all phases of the treatment of the patient, which must attend the successful use of local anaesthesia. He omits many of the seemingly small details which must be learned by experience and which often become the deciding factor in the operative test of the method. He emphasizes, however, the importance of adequate instruments for the accomplishment of the various procedures. He does not include material that is of historic or theoretic interest only, but presents his own practical experience with many thousands of cases.

The explanations of the methods are very clear both from the standpoint of anatomical approach and technical procedure. The illustrations are accurate and leave little to be desired.

E. M. H., Jr.

Practical Local Anesthesia and Its Surgical Technic. By ROBERT EMMETT FARR, M. D., F. A. C. S. *(Lea and Febiger: Philadelphia and New York, 1923.)*

Interest in local anaesthesia has been very slow to develop in the United States and Great Britain. Our surgeons have felt little need for improvement in our methods of general anaesthesia and have looked upon the dissatisfaction evidenced on the Continent as resulting possibly from the less skillful use of ether. The nurse anaesthetist has come to have an assured place in the great majority of our hospital clinics, and ether anaesthesia has been so satisfactory that few surgeons have felt the need for local or narco-local anaesthesia. Crile, however, saw a need for improvement and as a result developed his system of combined anaesthesia. He uses local anaesthesia more as an adjunct to nitrous-oxide, with the object of eliminating shock due to trauma of peripheral nerves. Farr, on the contrary, relies mainly on local anaesthesia, supplemented when necessary by light general narcosis.

Farr is one of the pioneers in this country in the extensive application of this type of anaesthesia to all branches of surgery, and his book is an excellent presentation of his experience.

The book is divided into three main parts, the first of which deals with practically all problems of anaesthesia, general and local, and discusses the arguments for and against each. Local anaesthesia is considered in great detail, with a presentation and description of the drugs used and the methods of induction. Farr believes that success with local anaesthesia depends on the effect of every point of contact between the patient and the hospital and gives his reasons for this belief. He describes the instruments he has evolved for the extensive use of local anaesthesia in his hospital, including an apparatus for the administration of novocain solution by means of compressed air. He points out that this apparatus eliminates much of the manual labor and loss of time which are often offered as an argument against local anaesthesia by its opponents.

In the second and third parts of the book the subject is considered regionally. Typical operations of practically every region of the body are described and short case reports are given. Methods of operative technique are not considered except when slight modifications or refinements will further the success of the method. The author devotes considerable space to the "anatomical, surgical and psychic factors which in the past were ignored, overlooked or unthought of by the novice and which account for the frequent early failures." Farr prefers infiltration anaesthesia and infiltration or conduction block. He also gives his experience with arterial, venous, and plexus block of the extremities, paravertebral block, and splanchnic anaesthesia. His use of spinal block has been limited.

The book is well written and well illustrated and offers much of value to the skilled local anaesthetist as well as to the novice.

E. M. H., Jr.

Mental Hygiene and the Public Health Nurse. By V. MAY MACDONALD, R. N. 6 Shillings. *(Philadelphia: J. B. Lippincott Company, 1923.)*

For the public health nurse, as the part of the health machinery most directly in contact with the field problems of mental hygiene, Miss MacDonald has attempted to formulate a program of field practice. In spite of the regrettably brief method of presentation—sixty-seven pages of text—the effort must be regarded as distinctly successful. The small volume will be of real value to public health nurses, to health officers, and to others interested in the subject.

The field of activity laid out for the nurse is wider, perhaps, than is justified, either by the previous training or the usual scope of the public health nurse's activities. Habit formation in children, sex education and the prevention of syphilis are not in themselves problems for the public health nurse.

Every public health nurse should, however, possess and read this little volume, not with the idea that she may thereby become a mental hygienist but with the belief that in the simple and sound presentation of the facts of mental hygiene which the volume contains will be found the answer to many practical problems encountered in the daily work in the field.

A. W. F.

Diathermy and Its Application to Pneumonia. By HARRY EATON STEWART, M. D. $3.00. *(New York, Paul B. Hoeber, Inc., 1923.)*

This little book is an interesting exposition of the method of diathermy—local internal concentration of heat by means of an electric current—in pneumonia and other conditions. One is favorably impressed by the mode of exposition, although, as in the case of the other procedures, no conclusive evidence of any fundamental curative effect is presented.

A. L. B.

Physical Diagnosis. By RICHARD C. CABOT, M. D. Professor of Medicine in Harvard University. $5.00. *(New York, William Wood and Company, 1923.)*

The physician or medical student contemplating the use of this book should carefully read the prefaces and then he will not be disappointed, as he will learn that this new, eighth edi-

tion, of this popular textbook is the summation of the author's diagnostic and interpretative methods. It is essentially an individual contribution to medical knowledge. This edition, as is explained in the preface, is similar to the previous ones, but has some valuable additions, and the text is written in the author's terse and forthright style.

As many another popular textbook that has gone through many editions, in some ways it has been improved, and in some other respects it seems inferior to former editions. For example, one misses the familiar face of the patient with argyria, and instead the frontispiece of this edition is a much less expensive half-tone of a radiograph showing a renal neoplasm. The former frontispiece would be much more likely to form a lasting mental impression. In general, the half-tones are less clearly reproduced than in former editions. Also, the book is marred by typographical and other errors, some of which have gone from edition to edition; for instance, Traube's semilunar space is correctly delimited in the first part of the book, and incorrectly outlined in the latter portion. This same error obtained in the sixth edition. One wonders whether the author still makes use of the fermentation test, published in this edition, as his method of choice for quantitative sugar determinations in the urine. And as a last statement in criticism, it seems unfortunate, if blood counting procedures are to be described at all, that the newer double counting chambers have not received the recognition unquestionably due their superior qualities. These, after all, are very minor points which could be easily corrected in a reprinting of this edition.

The fundamentals of physical diagnosis are very clearly stated, and the reader is not terrified by a tremendous volume of detail, nor is the exposition so sketchy as to disappoint the student. These diagnostic procedures and the clinical interpretations are described in an exceedingly straightforward manner. There is a very genuine appreciation of the relative value of the various technical methods and the diagnostic inferences that may be drawn from them. The author has been a very close student of the results of post-mortem examinations, and the curbing influence of the autopsy is seen throughout the book.

In conclusion, if the medical student or the practitioner is thoroughly conversant with the diagnostic methods and the interpretative reasoning set forth in this book, he will be very certain of all the usual and also of many of the less common clinical conditions. L. G.

Anatomy and Physiology for Junior Nurses. By Felice Norton. *(London: The Scientific Press, 1922.)*

Although supposedly dealing with anatomy and physiology, by far the bulk of the text is concerned with anatomy. In writing about the circulatory system the author says practically nothing about the pulse, and absolutely nothing about blood pressure.

Nor does the anatomy portion of the book make up in accuracy what the volume lacks in physiology. We learn, for instance, that the "meningeal artery" is the chief branch of the internal carotid artery; that the phrenic nerve innervates the muscles of respiration; and that lymphatics dip into brain substance.

The illustrations are also not always correct, e. g., Fig. 12.

It is of course possible that a short book of this nature may satisfy the British standards of nurse training, though it is difficult to believe that many American training schools would adopt it. F. C. L.

Arab Medicine and Surgery. A Study of the Healing Art in Algeria. By M. W. Hilton Simpson, B. Sc. $3.50. *(Oxford University Press, American Branch, New York.)*

We quote from the Preface:

"A layman—totally untrained in medical science—I suddenly found myself, in 1913, admitted to some of the secrets of the reticent Berber and Arab doctors of the Aures Massif, Algeria.

"It is my misfortune that I lacked the knowledge necessary to enable me to do justice to the opportunities of studying their art which I have enjoyed.

"But for the kindly interest taken in my work by the late Sir William Osler I should not have ventured to publish these notes at all."

A small book, full of interesting matter, does not lend itself readily to a short detailed review. Incidentally, the research worker, no matter in what branch, may learn from it (1) modesty, (2) how a research should be planned and carried out, and (3) how a mass of interesting and accurate observations can be condensed (without suffering loss) into some ninety pages, of which few are dull, many are good, and most are still better. F. R. S.

Neurologic Diagnosis. By L. E. Davis, M. D. $2.00. *(Philadelphia, W. B. Saunders Co., 1923.)*

This is a duodecimo volume. The first 45 of the 175 pages are devoted to the anatomy and physiology of the nervous system and a clinical discussion of nervous diseases. The rest of the book is given up to 29 case reports, which are clearly described, well analyzed and constitute the most valuable part of the book. There are 49 illustrative drawings, an index, but no bibliography.

The book is well written and contains a great deal of information, but is very much too compressed. For example, the anatomy of the motor tracts and disorders of motility are covered in eight pages. Less than one page is given to the discussion of aphasia and speech disorders. It is very doubtful whether the book will supply any real need, since it is too condensed for elementary students and offers nothing of value to anyone well acquainted with the subject. F. R. F.

Impotency, Sterility, and Artificial Impregnation. By Frank P. Davis. 2nd Ed., 168 pages, $2.25. *(St. Louis, C. V. Mosby Co., 1923.)*

There are few problems in medicine that are as engrossing and as vital as those which one encounters in the study and treatment of impotency and sterility. It was with keen anticipation, therefore, that the reviewer picked up this volume entitled "Impotency, Sterility and Artificial Impregnation;" but after reading it, it was with equally pronounced disappointment that he laid it down.

This is in reality a "sex-book" with a quite superficial smattering of psychology, unscientific gynecology and urology. It opens with a fifty-eight page discussion of the relation between the special senses and the sex instinct. These chapters, although entertaining, could hardly be called medical literature. Impotency, including "sensuality in women" and "race suicide," forms the subject matter of the next forty-four pages. The entire problem of sterility is presented in nineteen pages; and artificial impregnation, after being exalted by mention in the title of the volume, is summarily dismissed with six small pages of large print. After reading this book, one cannot help wondering why and for whose benefit it was written.

L. R. W.